A2ALL Core Protocol
Manual of Operations
Version 1.5
August 19, 2013

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1. GENERAL

1.1. Overview

The study Manual of Operations (MOO) is supplied to each participating site to aid in the conduct of the Adult-to-Adult Living Donor Liver (A2ALL) Transplantation Cohort Study Core Protocol.

Please refer to **Appendix A** to view the Core Protocol. Details not outlined in the protocol are in this manual. The current version of the MOO, and protocol documents are available on a website maintained by the Data Coordinating Center (DCC) at www.nih-a2all.org.

1.2. Sponsor

The A2ALL project is a cooperative research program sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a division of the National Institutes of Health (NIH). Averell H. Sherker, MD, and Jill P. Smith, MD are the NIDDK Project Officers.

1.3. Study Organization/Project History

The main goal of this project is to provide valuable information on the outcomes of living liver donation. In order to learn more about the risks and benefits of living liver donation, the project includes a group of clinical transplant centers and a Data Coordinating Center (DCC) to study a large number of people who have donated a liver for transplantation.

The project is a collaborative consortium consisting of nine clinical transplant centers, the NIDDK Project Officers, and a DCC. The Steering Committee is the governing body, consisting of the NIDDK Project Officers and the Principal Investigators (PIs) from each of the clinical sites and the DCC.

The consortium was originally formed in 2002 for an initial funding period of seven years. During that time, the project conducted a retrospective study, a prospective study, and several ancillary studies. Forty publications arose from this collaboration. The NIH decided to continue to support this consortium through a second funding cycle. This Core Protocol represents the first protocol of the second iteration of the A2ALL project (referred to throughout as A2ALL-2).

Please reference the Study Directory (**Appendix B**) for participating sites' contact information.

1.3.1. Data Coordinating Center (DCC)

The University of Michigan is the DCC for A2ALL. The DCC provides project management, logistical coordination, and statistical leadership for the development, implementation, and analysis of A2ALL-2 studies. In addition, the DCC will conduct training in protocol implementation, data management, monitoring, and quality control. The DCC also supports regulatory and technical functions (i.e., A2ALL website). For a list of DCC personnel and their roles and contact information, please refer to the Study Directory (**Appendix B**).

1.3.1.1. DCC Contact Information

- Peg Hill-Callahan, Project Manager – peg.hill-callahan@arborresearch.org, Phone: 734-369-9674
- All DCC – a2all-dcc@umich.edu
- Monitoring Staff – a2all-monitors@umich.edu
- Fax – 734-665-2103

1.3.2. Clinical Sites and Principal Investigators

Columbia University Medical Center
New York, NY
Principal Investigator: Jean C. Emond, MD

Northwestern University
Chicago, IL
Principal Investigator: Michael M.I. Abecassis, MD, MBA

University of Pennsylvania
Philadelphia, PA
Principal Investigator: Kim M. Olthoff, MD, FACS

University of Colorado Denver
Aurora, CO
Principal Investigator: James R. Burton, Jr., MD

University of California, San Francisco
San Francisco, CA
Principal Investigator: Chris E. Freise, MD, FACS

Virginia Commonwealth University – Medical College of Virginia
Richmond, VA
Principal Investigator: Robert A. Fisher, MD, FACS

Lahey Hospital and Medical Center
Burlington, MA
Principal Investigator: Elizabeth A. Pomfret, MD, PhD, FACS

University of Pittsburgh Medical Center
Pittsburgh, PA
Principal Investigator: Abhinav Humar, MD

University of Toronto
Toronto, ON, Canada
Principal Investigator: David Grant, MD, FRCSC

1.3.3. NIDDK Data Safety and Monitoring Board

The Data Safety and Monitoring Board (DSMB) meets two times a year to provide independent review of data safety and monitoring procedures for A2ALL-2 protocols. The DSMB may also convene to review the study protocol, if significant safety concerns arise. All protocols are reviewed and approved by the DSMB prior to implementation. The Board meets to examine endpoints, subject enrollment, protocol compliance, completion of samples and data, toxicity, and

safety data from NIDDK-supported protocols. Since the A2ALL Core Protocol is an observational study with no drug or other medical interventions, few adverse events related to study-mandated procedures are expected. Reference the DSMB Charter and DSMB Membership List (**Appendix C**) for additional information regarding the DSMB.

1.3.4. A2ALL Website

Publicly accessible information about the A2ALL project is available on the A2ALL website home page. Some portions of the website are password-controlled to limit access to study group members (Clinical Centers, DCC, NIDDK, and the DSMB), protect the integrity, security, and confidentiality of sensitive project information and the information system, and allow auditing of appropriate use.

The website contains workgroup/subcommittee member lists, meeting agendas, materials, and minutes, slides and presentations, master documents (including final protocols and consent templates), calendar of events, and study directory. The secure *A2ALL-Link* data entry system is also linked via the password-protected portion of the website, affording a double login/password for access to subject data.

1.3.5. Website URL and Access Instructions

The URL for the A2ALL website is http://www.nih-a2all.org/. Website management resides with the DCC. The DCC is responsible for login accounts, study directory updates, postings, and maintenance. Upon assigning a username and password, an automatic welcome email will be generated, informing the user that access has been granted to the restricted areas of the website. Users must change their system-assigned password within 72 hours of the welcome email receipt or website access will be denied.

Usernames and passwords should not be shared. New personnel requiring access to the A2ALL website should request a unique username and password. For new account requests or trouble with usernames and passwords, please contact Jenya Abramovich (jenya.abramovich@arborresearch.org/734-369-9679) at the DCC.

2. IRB SUBMISSION AND REGULATORY DOCUMENTS

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and the monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory standards. The minimum list of essential documents that has been developed follows.

2.1. Protocol Version Control, Finalization, and Approval Process

Protocol version control is extremely important to ensure that all participating sites and their respective Institutional Review Boards (IRBs) receive identical documents. Before a protocol is considered final and versioned (e.g., version 1.0), it must go through a formal review by the A2ALL Steering Committee. Once finalized, the protocol document,

consent templates, and any supplemental materials will be distributed to the sites by the DCC. Sites should submit only materials distributed by the DCC to their IRBs. Finalized protocols must NOT be edited, changed, or altered.

All amendments (a written description of a change(s) to or formal clarification of a protocol) must undergo a similar approval process. Sites should only submit protocols and amendments to IRBs as instructed by the DCC or NIDDK.

2.2. Consent Form Finalization and Approval Process

Protocol-specific consent document templates will be provided to all A2ALL-2 sites. Site-specific language should be inserted into the template. Please refer to **Appendix D** to view the Consent Templates.

Each site-specific informed consent form (**Donor and Recipient**) will be reviewed by the DCC for inclusion of all essential elements and compliance with Federal Regulations. After DCC review, the sites' draft informed consent documents will be reviewed by the NIDDK Bio-sample Repository staff. After that review, the NIDDK will return the draft consent to the DCC. The DCC will then return the reviewed/edited draft consents to the sites for correction and submission to the IRBs. Below is a set of instructions detailing the DCC review and approval process of the site-specific consent form(s).

The first six steps below must be completed prior to submitting any consent documents to the IRB.

1) Forward the informed consent (IC) documents to the DCC lead clinical monitor for review (beth.golden@arborresearch.org).
2) Once documents have been reviewed and changes made, the DCC will forward the informed consent documents to NIDDK (if consents meet criteria for need of NIDDK review).
3) The NIDDK Project Officers will forward the draft informed consent documents to the NIDDK Bio-sample Repository reviewers. Once they have reviewed them, the repository reviewers will send the informed consent documents back to the DCC for final corrections.
4) The DCC will return the reviewed/edited draft informed consent documents to the sites.
5) The site will make the required changes to the consent forms and send the revised consents to the DCC. The DCC will forward the revised consents to NIDDK for re-review and approval.
6) NIDDK will send an approval letter and the approved consents to the site PI and a copy to the DCC.
7) The site will submit the consent documents to its respective IRB.
8) The IRB may require changes to the consent form. Please forward requested changes to the DCC lead clinical monitor for review prior to resubmission to the IRB.
9) The IRB approval will be in the form of a letter or memo. The notification should include the title of the protocol, version number, PI name, and the IRB members. The memo should state that approval has been granted to open or continue the study.

Steps 2–6 are not necessary if the NIDDK is not involved in the review of amendment consents if the changes in the consent do not involve the NIDDK Bio-sample Repository.

File the IRB-approved consent document(s) (memo, consent, and other documents) in the site regulatory binder. Scan all approved documents and send electronically to the DCC. Throughout the course of the study, the DCC will request these documents when there is an amendment to the Core Protocol and at the time of each site's IRB annual renewal.

2.3. Certificates of Confidentiality

Certificates of Confidentiality constitute an important tool to protect the privacy of research study participants. Certificates of Confidentiality are issued by the NIH and/or the Food and Drug Administration (FDA) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants. For more information, please see the NIH's Certificate of Confidentiality Kiosk: http://grants.nih.gov/grants/policy/coc/

The DCC will obtain and maintain Certificates of Confidentiality for the study. These Certificates provide coverage to all clinical sites. Please refer to **Appendix E** to view the study's Certificates of Confidentiality.

2.4. Essential Documents for the Conduct of a Clinical Trial

Required regulatory documents are to be kept on file at the site. The regulatory binder must be kept current and available for review during site monitoring visits. Please refer to **Appendix F** for a list of Regulatory Binder tabs.

If the site maintains master files for CVs, lab normals, etc., then a note to file should be placed in the study-specific regulatory binder to reflect the location of the documents.

REMEMBER, WHEN THE STUDY IS FINISHED AND READY FOR ARCHIVING, ALL DOCUMENTS IN THE MASTER FILES MUST BE COPIED TO BE STUDY-SPECIFIC DURING THE CONDUCT OF THE TRIAL. THE DOCUMENTS WILL BE STORED FOR THE LENGTH OF TIME DESIGNATED BY THE SPONSOR.

The following documents must be maintained in the regulatory binder throughout the study:

1) **Study Protocol**
   - Maintain a copy of the original IRB/Ethics Research Committee (ERC)-approved protocol for the study and any subsequent IRB/ERC-approved revisions/amendments to the protocol.
   - Any changes to the protocol must be submitted to and approved by the IRB prior to implementation.
   - Include full copies of all final versions, stored in reverse chronological order with the current approved version first.
   - IRB/ERC submission/approval of revisions/amendments should be filed under Section IRB Approvals in the Regulatory Binder.

2) **Curriculum Vitae (CV): Investigators and Sub-Investigators**

- To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects. Ensure the CV is complete and contains the following information:
  - Current appointments/positions/citations, etc.
  - Start and end dates (or "to present") for all appointments and positions (no date gaps).
  - Signed and dated (on first page) by the investigator (or sub-investigator) and all study personnel to verify document is current.
- Updated CVs are to be filed bi-annually.
- CVs may be kept in a "Master File" during the conduct of the study, but all the CVs must be archived with the study at the end of the trial.

3) **Medical License**

- Maintain copies of all licenses for licensed personnel (e.g., MDs, Nurses, Nurse Practitioners, Physician Assistants, etc.) for the duration of the study.
- Licenses may be kept in a "Master File" during the conduct of the study, but all the licenses must be archived with the study at the end of the study.

4) **IRB Approval**

- Documentation of the provision of IRB/ERC review and approval of the protocol insures that the study is conducted with the appropriate local regulatory oversight. IRB/ERC approval will be obtained prior to the initiation of the study, and maintained throughout the conduct of the study and data analysis phase. Sites should maintain current IRB approval until directed by the DCC to close the study.
- All IRB/ERC approval letters must be on file. They include, but are not limited to the protocol, consent(s), study advertisement(s), training and educational materials, participant letters, questionnaires, or any other documents receiving IRB/ERC approval or opinion. All of these documents must be forwarded to the DCC. **NOTE:** If contingent approval is granted, evidence of final approval must be present before the study can be implemented.
- All annual or periodic renewals.
- Approval letter for any protocol amendments and modifications (the sponsor and the IRB/ERC must approve all protocol changes prior to implementation unless the change is intended to eliminate an apparent immediate hazard to subjects).
- Any local or country-specific regulatory authorization relating to the protocol.
- All approval letters from the IRB/ERC should be addressed to the principal investigator and should include the following information:
  - Protocol title, number, and version
  - Actual date of IRB/ERC approval
  - Specifically state approval of the protocol
  - IRB/ERC chairperson's or designee's signature
  - Renewal date or statement indicating when the approval must be renewed
  - List of the documents approved
  - List of all sites covered by the IRB/ERC approval

5) **IRB Membership List**

- The IRB/ERC's composition is constituted in agreement with Good Clinical Practice (GCP).
- IRB/ERC information including membership list, chairperson, and general

assurance number or a letter stating that the IRB is in compliance with GCPs.

- IRB membership list must be current.
    - If your IRB/ERC does not release its membership list, a DHHS Multiple Assurance Number must be submitted on the IRB/ERC letterhead.
    - If the IRB does not allow access to their membership list, then an anecdotal note must be written to reflect the standard operating procedure of the IRB and the note must be filed in the regulatory binder.

6) **Study Monitoring Log**

- The log is populated with the signatures of those individuals overseeing (monitoring) the progress of the clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirements. It provides documentation at the site that the study was monitored and the frequency of the monitoring.
- Maintain a study-specific monitoring log at each site. The monitor's dated signature should be included for each visit, and signed off by the designated site staff (study coordinator) for each monitoring visit. For consecutive days, each day is entered separately.
- A copy of the monitoring log will be taken by the monitors for filing at the DCC.
- Maintain a copy of all monitoring/site visit letters and reports.
- Maintain a copy of all correspondence concerning monitoring visits.
- Included as appendix to regulatory binder. Included in MOO as **Appendix G**.

7) **Subject Screening Log**

- Maintain a subject screening log throughout the course of the study.
- Screening log contains information (including reason for screen failure) regarding all potential patients approached (entered pretrial screening) for participation in the study and the outcome of that encounter. Please refer to Section 8 for further details about eligibility.
- Click on the appropriate answers found in the drop-down choices in each column when completing the screening log. The comment column is the only column that allows for free text. This enables the DCC to filter/sort subject information in the log for the collation of data for the weekly A2ALL Core Protocol Enrollment Report.
- The DCC will provide an electronic (Excel) file of the blank screening log. The completed file should be emailed to the DCC (a2all-monitors@umich.edu) on every Monday.
    - The DCC will not accept faxed copies of the screening log. It must be transmitted electronically.
    - There are screening log definitions which define the outcome of potential subjects for enrollment into the Core Study. definitions are as follows:
        - *Approached–Refused*: The subject refuses to consent to the study
        - *Approached–Dead*: Contact is attempted and it is discovered that the subject has died
        - *Approached–Lost to Follow-up*: Contact is attempted and the subject cannot be found

- *Approached–Unresponsive*: Contact is attempted to a known correct address/phone number and subject does not respond
- *Not Approached–Language Barrier*: Subject has a language barrier that would make obtaining consent and conducting the study impossible, or it is an HRQOL-only subject who does not speak English
- *Not Approached–Staffing Issues*: An eligible subject is in-house or otherwise available for approach and due to a problem related to study administration is not approached (coordinator misses patient while s/he is in clinic)
- *Inclusion/Exclusion Criteria*: A subject formerly thought to be eligible is not (former Cohort subject who has had another transplant)
- *Other*: when this option is used, a comment must be entered onto screening log

- When a Core subject consents to the Core Protocol only, and refuses the HRQOL portion of the study, enter the refusal reason (if available) in the comments section of the screening log.
- Included in the MOO as **Appendix H**.

8) **Roles and Responsibilities**

- Contains the list of all study personnel who are involved in the primary conduct of the trial at the site. It documents responsibilities assigned to research team members and their dates of involvement in the project. It helps to ensure the appropriate delegation of study related tasks, and documents authenticity of the written signature of personnel involved in the conduct of the study.
- Maintain a list of all study personnel on appropriate form and include:
  - Initials
  - Printed name
  - Legal signature, including first and last name
  - List of delegated responsibilities
  - Start and end date for delegated responsibilities
- Included as appendix to regulatory binder. Included in MOO as **Appendix I**.

9) **Human Subjects Research Certification**

- All investigators, sub-investigators, and study personnel listed on the delegation of responsibilities log must complete research ethics training.
- Any course on the protection of human subjects provided by your institution will meet this requirement. The course title, student's name, and dates of completion and expiration (if applicable) must be on the certificate. A brief description of the course must also be placed on file. If the site-specific course is one that does not expire, this should be outlined in the description provided.
- Training and certification can also be obtained at the following website:
  - NIH: Protection of Human Research Subjects – http://ohsr.od.nih.gov
- New study personnel must complete all of the required human subjects training, and their addition must be approved by the IRB prior to their participating in the study.

10) **Safety Reporting – Serious Adverse Event (SAE)**

- An SAE is any untoward study-related medical occurrence that occurs during the trial.

- Report all SAEs to the DCC within 24 hours using *A2ALL-Link* (Please see protocol for reporting SAEs).
- Notify your IRB of all SAEs, as per their guidelines.
- Maintain copies of the SAE report forms.
- Maintain documentation of notification of all SAEs to the IRB.
- The World Health Organization (WHO) grading scale for SAEs is included in Protocol Version 2.1 as Appendix C.

11) **Major Sponsor, DCC, and IRB Correspondence**

- Maintain a copy of all correspondence (e-mails, letters, faxes, memoranda, and phone contacts) between the investigator or research staff, Sponsor, and DCC relating to the **clinical** conduct of the study, especially correspondence pertaining to:
    - Site activation letter
    - Protocol decisions (by phone or e-mail)
    - Serious adverse events
    - Deaths
    - Protocol deviations
    - Protocol modifications
    - DSMB roster and letters from the Project Officer
    - Site monitoring reports
- Maintain a copy of all pertinent communications with the IRB/ERC relating to the study (e.g., Study Hold, Safety Report, Removal of Subject, Protocol Deviation, and Notice of Final Study Report).

12) **Investigator Signature Page (page 2 of protocol)**

- Documents investigator and sponsor agreement to the protocol and/or amendment(s).
- Site principal investigators are required to sign page two of the protocol.
- The site principal investigator must sign a new signature page for any amendment.
- Submit a scanned copy to the DCC (jenya.abramovich@arborresearch.org) and file the original in this section.

13) **IRB-Approved Informed Consent (IC) Forms**

- Maintain copies of the original IRB/ERC approval and any subsequent IRB/ERC approved revisions/amendments to IC or consent addenda. Additional consent documents (e.g., screening consents) should be obtained per site requirements.
- Maintain copies of translated ICs with their back translation for any form prepared in a language other than English. This must include a certificate of translation.
- Ensure that a version number and date is included on all consent documents.
- Include IRB approval letter with the IC if the IRB does not stamp the document.
- IRB approved consent documents should not be altered by the subject or study staff personnel during the consenting process. Check-offs, signatures, and dates are the only pieces of information that need to be written in on the consent. Crossing out sections or adding additional comments in the consent are not allowed according to federal regulations.
- Consent form documents must be stored in reverse chronological order with the current approved version first. Place the most currently approved consent

form(s) in a plastic sleeve. **NOTE**: Any changes to the consent form must be submitted to, and approved by the IRB prior to use.

14) **Laboratory Documentation**

- Documents that laboratory tests are performed with appropriate care and oversight throughout the trial period.
- Each site laboratory's current certification(s), Clinical Laboratory Improvement Amendment (CLIA), College of American Pathologists (CAP) and all previous certification(s).
- CLIA exemptions for certain laboratory tests should be documented.
- Place note-to-file in the regulatory binder if either the CLIA and/or CAP certifications have expired, and the site is waiting for the renewal certification.

15) **Normal Laboratory Ranges**

- Documents normal values and ranges (including revised) that were used during the conduct of the clinical trial.
- Record of current laboratory normal ranges. All units of measurement, the laboratory name, and document date should be included.
- Provide updates as necessary and retain the original document.
- Place a note-to-file in the regulatory binder to indicate if laboratory normals are kept in a Master File to reference.
- Copies of laboratory normals used during the conduct of the trial must be taken out of the Master File and placed in the study's archival file at the end of the study.

16) **Certificates of Confidentiality**

- Certificates of Confidentiality are issued by the NIH and/or the FDA to protect the privacy of research subjects by protecting investigators and institutions from being compelled to release information that could be used to identify subjects with a research project.
- Certificates of Confidentiality are issued to institutions or universities where the research is conducted. They allow the investigator and others who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- The lead institution must ensure that all participating institutions conform to the application assurances and inform participants appropriately about the Certificate, its protections, and the circumstances in which voluntary disclosures would be made. This information is built into the template consents for the study.
- The Certificates of Confidentiality can be downloaded and printed from the study website in the Master Documents area.
- Certificates of Confidentiality receive modification when changes are made in the study and must be approved/signed off by the Certificate Coordinator at NIDDK.
- New Certificates of Confidentiality are generated by the Certificate Coordinator following review and approval of the modifications to the study.
- Print the Certificates and keep the copies in your regulatory binder.

17) **Certification for Shipment of Bio-samples**

- Each site must have at least one person certified to ship bio-samples, and the certification (HAZMAT) must be current.

- Names of the research staff that are certified, and a copy of the certificate, should be maintained in your regulatory binder.

18) **Advertisements/Educational Materials**

- After IRB approval, maintain copies of all advertisements (e.g., fliers, radio announcements, newspaper/internet advertisements) and educational materials (e.g., slide shows) utilized for the study.
- All materials filed in this section and used in the study should be IRB approved and clearly listed on IRB approval letters/notices.

CVs, medical licenses, IRB approvals, laboratory certifications/accreditations should be kept current. Current copies of required documents (IRB approvals) should be forwarded electronically to the DCC when available. The DCC will assist sites in monitoring IRB, CV, and license expirations.

3. SITE TRAINING AND ACTIVATION

3.1. Site Training

Site staff will receive study training prior to implementation of the study. Reference the Site Training Slides in **Appendix J** for additional information. Training will include, but not be limited to, review of:

- Main protocol and sub-studies
- Health Related Quality of Life (HRQOL) implementation
- Informed consent process
- MOO
- Data collection electronic Case Report Forms (eCRFs)
- Schedule of events
- Study-specific procedures
- Collecting, processing, labeling, shipping, and tracking of bio-samples
- Use of *A2ALL-Link*
- Site initiations and monitoring plan

Please notify the DCC of new study team personnel so they can receive the appropriate training and web access.

3.2. Site Activation

Upon verification of required regulatory documents, training requirements, and a site initiation visit, the site will receive a study activation letter from the DCC indicating that study activities may begin the conduct of the study. A copy of this letter should be filed in the regulatory binder behind the appropriate tab. This letter documents that the trial procedures were reviewed with the investigator and investigator's staff and that the site is suitable for the trial. The site may not recruit subjects or collect data prior to receiving the activation letter.

4. STUDY MONITORING

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accorandance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirement(s). Monitoring will include a combination of annual site visits and remote monitoring. Monitoring helps to catch problems and noncompliance before the actions become repetitive. It can identify systemic issues which can be corrected before a study is jeopardized.

Remote monitoring will occur at the DCC, and site-specific information in the form of reports reflecting data completion, integrity, and quality will be produced. These reports will be generated at least monthly and will be shared with the sites and NIDDK.

The DCC will produce reports showing:

- Overall data completion
- Data entry timeliness
- Form completeness
- Database queries comprised of logic checks
- Outstanding queries
- Bio-sample shipping
- Bio-sample collection
- Enrollment with consent status (including entire history of consent)
- Protocol deviations
- Visit completion
- Number (%) of queries resolved
- Number (%) of queries per study subject
- Regulatory review
- Other issues identified
    - Best practices identified
    - Areas for improvement
    - Strategies for improvement
    - Barriers to success at site
    - Regular attendance at study coordinator calls

The DCC will also request a sample of de-identified source documents from the site to check for transcription errors in the database. The DCC staff may conduct site management calls, if needed, to ensure data quality compliance and data query resolution.

The DCC will schedule a site visit with each site PI and study research staff on an annual basis. During the Site Monitoring Visit, the site's performance on the metrics described above will be discussed. The coordinator(s) and PI must be available for the conduct of the visit to be successful. The agenda for the visit will include such topics as:

- Essential elements of protocol adherence
- Recruitment and retention strategies
- Regulatory document requirements
- Completeness or missingness of visits, forms, data, and samples
- Responses to data queries
- Identifying, discussing, and developing strategies for eliminating barriers to recruitment, retention, and protocol compliance

- Electronic Case Report Forms (eCRFs) and source documents*
- Study-specific training (e.g., *A2ALL-Link*)
- Identification of best practices
- Additional monitoring activities, including more frequent on-site monitoring, may be scheduled at the request of NIDDK, the DCC, or the site PI.

*Source Documents: original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, x-rays, and subject files) kept at various departments involved in the clinical trial.

On the last day of the monitoring visit, a "wrap up session" will be held at the site as a conference call. The attendees of the conference call will include (but are not limited to): site PI, site study coordinator(s), DCC clinical monitors, DCC PI or DCC clinician, DCC Project Manager and administrative staff, and NIDDK Project Officers. The purpose of this call is to review the findings of the visit prior to the release of the final site monitoring report. The call will be scheduled at the same time the visit is confirmed.

A site monitoring report summarizing the visit and findings will be generated by the monitor(s) and DCC clinician (if in attendance) conducting the visit. The report will contain detailed accounting of the visit findings, steps taken to resolve issues, and any outstanding issues the site needs to address prior to the next visit. The post-visit report will be sent to the site PI and NIDDK. The NIDDK Project Officers may choose to share the monitoring report with the DSMB. The study coordinator(s) will receive a copy of the report. The monitoring report is to be filed in the the Correspondence section of the site's regulatory binder.

When a site has consistent, repeated deficiencies in one or more areas, the DCC will discuss the issues with NIDDK and the study PI. The findings will be noted and may include a request for a remedial action plan. The plan should explain actions to correct the problem, indicate implementation of preventative actions to avoid recurrences, and timelines for the implementaiton. This plan will involve approval of the sponsor and study PI. Other means of remediation are to increase the level of monitoring focusing on the areas of difficulty.

Information on site monitoring as well as remote monitoring is included in the MOO in **Appendix K**.

5. OBTAINING & DOCUMENTING INFORMED CONSENT

5.1. Informed Consent Process

A signed IRB-, DCC-, and NIDDK-approved informed consent document must be obtained from each subject. Written consent should only be obtained after the PI or physician delegate is confident that the subject or legal guardian understands the information presented to the subject.

An investigator or their designee shall seek consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence.

5.1.1. Re-consenting Subjects Due to Amendments to the Protocol

The PI at each site determines the need for re-consenting based on the protocol amendment and the subject population. In the case of uncertainty on the part of the principal investigator, the site's IRB should be consulted.

5.1.2. Consenting Non-English Speaking Subjects

Per 21 CFR 50, the informed consent document should be in a language understandable to the subject (or authorized representative). Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective. A "short form" written consent document, in a language the subject understands, should be used to document that the elements of informed consent were presented orally. Local IRB guidelines should be followed. Maintain copies of translated ICs with their back translation for any form prepared in a language other than English. This must include a certificate of translation.

Subjects who cannot read and write English are specifically excluded from the HRQOL and Donor Pain arms of the Core Protocol.

5.2. Documentation

Site personnel must document in the subject's medical record that the subject has signed the informed consent, met enrollment criteria, and was enrolled into the A2ALL-2 Core Protocol study. Other pertinent details of the consent process, including summaries of telephone conversations with subjects, must also be carefully documented in the medical record. Refer to **Appendix L** for the form that documents the informed consent process.

The signed informed consent document should be maintained in the following locations:

- The original form is placed in the subject's research file.
- A copy is to be placed in the subject's medical chart.
- Subject or legal guardian will receive a copy.

Master files of signed consents at the sites are not condoned. All the subject's study related documents are to be maintained in the subject's research file.

5.3. Subject Identification Numbers

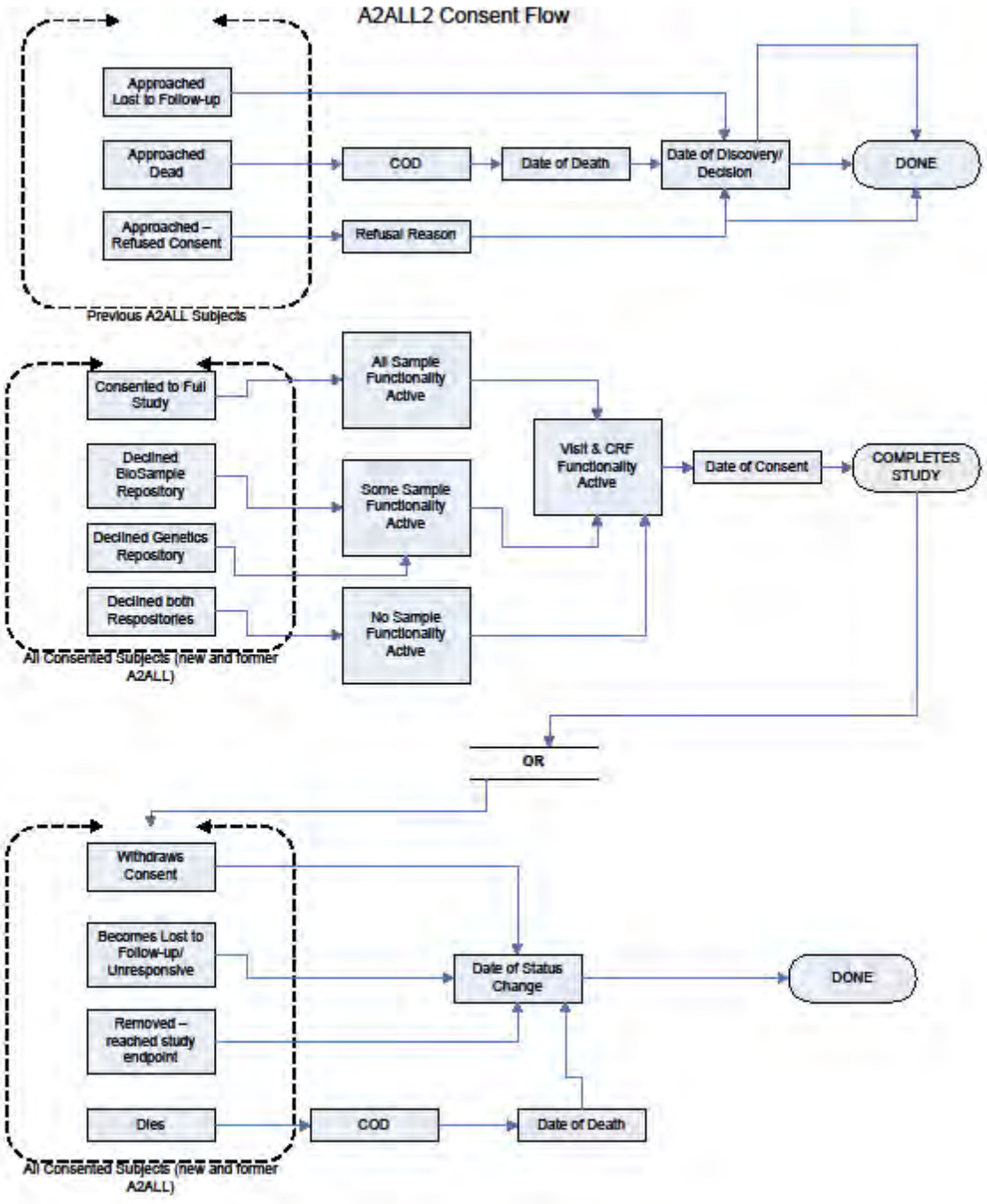
The subjects in the A2ALL-2 Core Protocol study will have a unique subject identification number. This number is created by *A2ALL-Link.* Subjects who were formerly in the A2ALL-1 Prospective Cohort study will retain the same study ID numbers assigned them for the Cohort study.

5.4. Definition of Consent Statuses

- *Consented to the Study*: consented to all aspects of the study as outlined in the consent
- *Refused Bio-sample Repository*: agreed to all aspects of the study (including Genetics Repository) EXCEPT bio-sample collection and storage at NIDDK

- *Refused Genetics Repository*: agreed to all aspects of the study (including Bio-sample Repository) EXCEPT genetics collection and storage at NIDDK
- *Refused both Bio-sample and Genetics Repository*: agreed to everything except genetics and bio-sample collection and storage
- *Dead*: use when a consented subject dies during the course of the study
- *Approached–Dead*: use when a former Cohort subject's death is discovered when you try to contact for consent
- *Approached–Lost to Follow-up/Unresponsive*: use when you have exhausted all routes to contact a former Cohort subject for consent and document Lost to Follow-up reason (if known) in dialog box. Also use when you approach a former Cohort subject for consent, the contact information is correct, but the subject does not respond to your efforts.
- *Approached–Refused Consent*: use when you approach a former Cohort subject for consent, and they refuse all aspects of study (document reasons for consent refusal in dialog box)
- *Removed-Reached Study Endpoint*: use when a consented subject reaches an endpoint prior to completing all study visits. Examples include:
    - Donation or transplant (TXP) surgery abortion
    - Recipient gets Deceased Donor Liver Transplant (DDLT) after being evaluated to receive a living donor liver transplant
    - Recipient no longer eligible for Living Donor Liver Transplant (LDLT)
    - When a former Cohort subject is being approached for enrollment and it has been discovered this subject has been re-transplanted prior to the beginning of the Core Protocol
- *Withdrew Consent*: use when a consented subject withdraws consent
- *Subject Entered by Mistake*: use when an inappropriate subject type was entered (e.g., entered a donor when it is a recipient, or when a potential HCVonly subject is deemed ineligible)
- *Waiver of Consent*: use for Amendment #2 V2.0
    - Liver transplant recipients with a hepatitis (HCV) diagnosis who are now deceased, had a graft failure, or who did not undergo the study biopsy
    - Transplant recipients and liver donors who reached a study endpoint (death, re-transplant, graft failure or transplant (donors) during the "Gap Era"
    - Deceased liver donors who donated to HCV recipients

5.5. Consent Flow Diagram



This diagram does not include the HCV-only group of subjects

6. PROTOCOL & APPENDICES

Please refer to **Appendix A** for the Core Protocol and associated appendices.

Sub-study Information

6.1. Health Related Quality of Life (HRQOL) Study

Primary Aim 3: To determine the prevalence, course, and predictors of poor HRQOL outcomes associated with living liver donation.

6.1.1. Eligibility Criteria

- Inclusion Criteria:
  - All donors previously enrolled in A2ALL will be eligible if they are now >2 years post-donation and donated in 2002 or later.
  - All donors from new A2ALL sites who meet these criteria will also be eligible. They will be enrolled utilizing the procedures specified in the study.

- Exclusion Criteria:
  - Inability to comprehend spoken English

6.1.2. HRQOL Survey Question Information

The following tables provide a key to link survey questions to the scales and domains they measure. We have provided tables for the (a) Long-term follow-up cohort (4 assessments: Time 1, Time 2, Time 3, and Time 4) and (b) Prospective cohort (5 assessments: pre-donation, and 3 months, 6 months, 1 year, and 2 years post-donation).

Each table lists the domain to be assessed, the specific survey items that assess the domain, and the total number of items to be assessed within the domain. In addition, the total time to administer the survey—based on early pilot testing—is included.

Long-term follow-up cohort, Time 1

Domain	Specific Items in Survey	Total No. of Items
Demographic items	34, 42, 43, 57 – 60	7
Mental health • PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)	39a-i, 40a-g, 41, 41a-e	11 to 22**
Somatic complaints • FACIT-Fatigue • Brief Pain Inventory Short Form: numeric rating + activity impairment subscale • Post-Donation Symptom Checklist • Post-Donation concerns about health (Simmons Worries about Donation items, Simmons Donation Stressfulness items; general QOL physical items)	 29a-m 28, 28a-g 27a-s 1, 9-15, 51, 52, 54, 61	 13 1 to 8 ** 19 12
Interpersonal relationships • Relationship with Recipient items (Simmons and general QOL items) • Simmons Family Support items • Simmons Worry about Recipient item • Toronto Recipient Behavior item • Simmons Preoccupation items • Simmons Grief items	 30, 32, 32e-j 33, 35 32d 32k 7, 31 32a-c	 2-14** 1-2** 1** 1** 2 4**
Financial concerns • Financial Burden of Donation items	 44-48, 49a-d, 50	 10
Positive psychological outcomes • Simmons Better Person scale items • Simmons Satisfaction with donating items • Campbell Global Life Satisfaction item • Regret item from general QOL items • Posttraumatic Growth Inventory	 2-6, 36a-c, 55, 56 8a-g 38 53 37a-j	 10 7 1 1 10
Generic HRQOL • SF-36v2	16, 17, 18a-j, 19a-d, 20a-c, 21-23, 24a-i, 25, 26a-d	36
Total No. of items/duration of assessment		146 to 176** 25 to 40 min***

*Most of the measures and items are copyrighted and are reproduced with permission
**Depending on whether respondent skips out of sections
***Estimate based on pilot testing

Long-term follow-up cohort, Time 2, Time 3, Time 4

Long-term follow-ups at Time 2, Time 3, and Time 4 are identical to those at Time 1 except that (a) item 10 about the recovery and two demographic items (education, ethnicity) are omitted and (b) the timeframe of some items is changed to the past year.

704 **Prospective cohort, Pre-donation**

Domain	Specific Items in Survey	Total No. of Items
Demographic items	63-68	6
Pre-donation factors/Risk factors • Simmons Psychosocial Background items (volunteer/donation history, importance of religion) • Simmons Donation Decision-Making items/scales (decision process, ambivalence, others' influence, anticipated outcomes, black sheep donor) • Simmons Preparedness for Donation item • General QOL pressure to donate items • Simmons Motivation for Donating Scale items	 22-27 1-13, 15-19, 30, 31, 50, 52, 57a-c, 58a-b, 59-61 62 14 28a-k	 6 30 1 1 11
Mental health • PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)	54a-i, 55a-g, 56, 56a-e	11 to 22**
Somatic complaints • FACIT-Fatigue • Brief Pain Inventory Short Form: numeric rating + activity impairment subscale • Donation concerns about health and well-being (Simmons Concerns about Donation items, general physical item)	 47a-m 46, 46a-g 34, 48, 49, 51, 69	 13 1 to 8** 5
Interpersonal relationships • Relationship with Recipient items (Simmons items) • Simmons Family Support items	 29a-d 32, 33	 4 2
Positive psychological status • Simmons Better Person scale items • Campbell Global Life Satisfaction item	 20-21 51	 2 1
Generic HRQOL • SF-36v2	35, 36, 37a-j, 38a-d, 39a-c, 40-42, 43a-i, 44, 45a-d	36
Total No. of items/duration of assessment		130 to 148/** 23 to 29 min***

705 **Depending on whether respondent skips out of sections
706 ***Estimate based on pilot testing

707

Prospective cohort, 3 months, 6 months post-donation

Domain	Specific Items in Survey	Total No. of Items
Demographic items	34, 41, 42, 56, 57	5
Mental health • PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)	38a-i, 39a-g, 40, 40a-e	11 to 22**
Somatic complaints • FACIT-Fatigue • Brief Pain Inventory Short Form: numeric rating + activity impairment subscale • Post-Donation Symptom Checklist • Post-Donation concerns about health (Simmons Worries about Donation items, Simmons Donation Stressfulness items; general QOL physical items)	 29a-m 28, 28a-g 27a-s 1, 9-15, 50, 51, 53, 58	 13 1 to 8** 19 12
Interpersonal relationships • Relationship with Recipient items (Simmons and general QOL items) • Simmons Family Support items • Simmons Worry about Recipient item • Toronto Recipient Behavior item • Simmons Preoccupation items • Simmons Grief items	 30, 32, 32e-j 33, 35 32d 32k 7, 31 32a-c	 2-14** 1-2** 1** 1** 2 4**
Financial concerns • Financial Burden of Donation items	 43-47, 48a-d, 49	 10
Positive psychological outcomes • Simmons Better Person scale items • Simmons Satisfaction with donating items • Campbell Global Life Satisfaction item • Regret item from general QOL items • Posttraumatic Growth Inventory (10 items)	 2-6, 36a-c, 54, 55 8a-g 37 52 Not asked at these time points	 10 7 1 1
Generic HRQOL • SF-36v2	16, 17, 18a-j, 19a-d, 20a-c, 21-23, 24a-i, 25, 26a-d	36
Total No. of items/duration of assessment		136 to 166/** 24 to 38 min***

**Depending on whether respondent skips out of sections
***Estimate based on pilot testing

Prospective cohort, 1 year and 2 years post-donation

These assessments are identical to those at 3 months and 6 months in the prospective cohort, except that the 10-item Posttraumatic Growth Inventory is included. This will increase the estimated time to 26 to 40 minutes.

To view the full surveys, please refer to **Appendix M**.

6.1.3. Enrollment of Long-term Donors for the HRQOL Study

6.1.3.1. A2ALL Long-term Follow-up HRQOL Study

Prior to the anniversary of the donation date for a liver donor eligible for the long term donor study, contact should be made to enroll them in the study and upload their contact information into the Survey Center web portals (at either Northwestern or Pitt) so they can be called by the survey interviewers within one month of the anniversary of their donation. We suggest that you begin to contact

eligible donors two months before their donation anniversary to give several weeks to establish contact, allow participants to opt out if that is your method of contact, and provide ample time for the interviewers to arrange for an interview within the time frame of assessment.

After your center is approved by the DCC to begin enrollment we suggest that you use the calendar below to identify the correct individuals to be enrolled at any given time point. Donors need to be two years since donation to be enrolled, and they have to have donated in 2002 or more recently.

IMPORTANT: The enrollment period for the long-term follow-up study is only 12 months. It extends from the time your center begins enrollment into the long-term follow-up study to the time you reach 12 months later. After that period, you would not identify additional donors but you would need to continue to try to enroll any donors that you had not finished attempting to contact during the 12-month enrollment window. If the survey centers are having difficulty reaching a donor from your center we may ask your assistance to locate them and update any contact information.

Long-term follow-up donors will complete up to 4 interviewers by the survey research team. As soon as the final interview is completed (or in the last year of A2ALL funding, whichever comes first), you will be asked to complete the medical records review for the required data on these donors and their recipients.

Enrollment Calendar: Months of enrollment and the years of donation eligible for enrollment					
In February-March 2011 enroll those who donated in the month April in the years 2002 to 2009	In March-April 2011 enroll those who donated in the month of May in the years 2002 to 2009	In April-May 2011 enroll those who donated in the month of June in the years 2002 to 2009	In May-June 2011 enroll those who donated in the month of July in the years 2002 to 2009	In June-July 2011 enroll those who donated in the month of August in the years 2002 to 2009	In July-August 2011 enroll those who donated in the month of September in the years 2002 to 2009
In August-September 2011 enroll those who donated in October in the years 2002 to 2009	September-October 2011 enroll those who donated in November in the years 2002 to 2009	October-November 2011 enroll those who donated in December in the years 2002 to 2009	In November-December 2011 enroll those who donated in January in the years 2002 to 2010	In December 2011 to January 2012 enroll those who donated in February in the years 2002 to 2010	In January-February 2012 enroll those who donated in March in the years 2002 to 2010 Stop when you've enrolled for the 12 month period

6.1.3.2. Finding Persons Who Are Lost to Follow-up

1) **Information That May Be Helpful for Your Search** (in roughly decreasing order of importance)
    - Full name (including middle name or initial)
    - Previous address
    - Phone number(s)
    - Date of birth/age
    - Gender
    - Race
    - Marital status

- Occupation or line of work

2) **Free Online People-Finding Resources**
   - google.com – Use quotation marks or parentheses around a full name. Often the simplest strategies are the most successful.
   - pipl.com – Pipl provides links to contact information, personal and professional profiles, public records, publications, photos, and videos matching your search criteria.
   - usps.com – The zip code lookup feature is useful for finding correct zip codes as well as detecting minor address errors (drive instead of road, etc).
   - mapquest.com – Like the postal service zip code finder, MapQuest may be helpful in finding street names that are similar to the address you have. You can enter the zip code or city and state to view a map of the area and look for similar street names.
   - Social Media – facebook.com, myspace.com, twitter.com
   - County Property Records – You may have to search by address instead of name, but you will be able to tell if the individual ever owned the property or if it has been sold.

3) **Additional resources**
   - whitepages.com
   - spokeo.com
   - zabasearch.com
   - anywho.com
   - County Court Records
   - Social Security Death Index (available through various websites, e.g., rootsweb.com)

4) **Resources that can be helpful if you can pay for the search**
   - peoplefinder.com
   - ussearch.com

6.1.4. HRQOL Survey Administration

6.1.4.1. Information

The study will utilize telephone-based survey methods to collect data at each assessment time point. A centralized approach to data collection will be utilized in order to maximize response rates and retention in the study. Thus, donors will be informed during the re-consenting process (or initial consenting for donors from new A2ALL sites) that their contact information will be forwarded to the survey research center responsible for data collection, and survey center personnel will then contact each donor to complete the telephone surveys.

All donors previously enrolled in A2ALL will be eligible if they are now >2 years post-donation (or become so during the period of A2ALL-2 funding) and donated in 2002 or later. All donors from new A2ALL sites who meet these criteria will also be eligible. They will be enrolled utilizing the procedures specified above.

All prospective donors at A2ALL-2 sites will be consented by a member of the A2ALL team located at those sites for general participation in A2ALL. The consent form will specify that, for the HRQOL sub-study, their contact information

will be provided to the survey research center that will be calling them to conduct the telephone surveys. The study will utilize telephone-based survey methods to collect data at a total of 5 assessment time points across 2 years post-donation, with the surveys administered by survey research center personnel.

After informed consent is obtained by staff at individual centers, all assessments will be conducted by telephone; no visits will be required. As noted above, donors will complete a maximum of 4/5 assessments, depending upon whether they meet criteria to be reassessed beyond the baseline assessment.

For further assistance please see **Appendix M**.

6.1.4.2. Transmitting Subject Contact Information to Survey Research Centers

The following sites will utilize the Northwestern University's survey research center for the HRQOL survey administration:

- Columbia University
- Northwestern University
- University of California at San Francisco
- University of Colorado
- University of Pennsylvania
- Virginia Commonwealth University

The following sites will utilize the University of Pittsburgh's survey research center for the HRQOL survey administration:

- Lahey Hospital and Medical Center
- University of Pittsburgh
- University of Toronto

The following information is provided to the survey centers for all donor subjects:

- Name
- Address
- All telephone numbers
- Email addresses
- Consent date
- Date of donation (or anticipated date of donation)
- A2ALL ID

If a subject is withdrawn from the Core study, either through subject's withdrawal of consent or due to a protocol violation, the site must notify the survey center. The site coordinator must ensure there is documentation of the notification of the survey center of the subject's withdrawal in the subject's research file.

Data entered prior to the subject's withdrawal stays in the database, but the subject is no longer contacted by the HRQOL survey administration staff.

6.2. Hepatitis C Virus (HCV) Study

Primary Aim 5: To compare the long-term histological outcomes in recipients of LDLT and DDLT with recurrent HCV Infection.

6.2.1. Study Population

- **Continuing Sites – eligible subjects who are already in Core**
  - Must be at least 3 years post-transplant and meet all of the eligibility criteria.
  - Question A5 on the RCP Study Entry Information eCRF must be answered "yes" for HCV diagnosis. (Recipient Diagnoses: Please answer for each diagnosis) Choose the diagnosis that best describes the reason for transplantation, and you may choose more than one diagnosis listed in the eCRF.
  - Fields completed in Cohort (BioDBx) will be pre-populated in *A2ALL-Link*.

- **Continuing Sites – HCV-only subjects who were not eligible for Core**
  - These subjects will be considered "HCV-only".
  - Includes dead and re-transplanted subjects (if death or re-transplant occurred more than 90 days post-transplant).
  - Will be uploaded into *A2ALL-Link* and will appear on your subject list.
  - Fields completed in Cohort (BioDBx) will be pre-populated in *A2ALL-Link*.
  - Dead and lost to follow-up subjects will have data collected via waiver of consent.
  - Re-transplanted subject's data are collected under a waiver of consent. Some of these subjects might have already been approached for the Core study, but were excluded when it was discovered they had reached an end point (re-transplant). If the subject was re-transplanted, and it was documented in Cohort, then this subject will be newly uploaded to your subject roster.

- **New Sites**
  - Eligible subjects will be entered as new subjects, designated "HCV-only" in the database in the consent dialog box (unless Core-eligible Gap).
  - Gap DDLT recipients will be "HCV-only" at new sites.
  - Dead, re-transplanted, and lost to follow-up subjects will have data collected via waiver of consent.

Please note, that no prospective Core subject will be eligible for the HCV study because they will not have achieved the 3 year post-transplant mark prior to the study's completion. No HCV eCRFs will be collected on any Core HCV subjects who die less than 3 years post-transplant either.

6.2.2. Consenting Subjects & Waiver of Consent

Core subjects consent to this sub-study as part of the Core Protocol study consent approved as part of Amendments #2 and #3 (includes HCV sub-study with waiver of consent). Eligible HCV subjects who did not sign the consent for Amendment #2 will need to be re-consented with the approved consent for Amendment #3. When entering the new re-consented information into *A2ALL-Link*, you should update the consent status, choose "consented to full study" (or other appropriate status), and enter the new date.

HCV-only subjects should sign the HCV-only consent (new sites only) that was approved as part of Amendments #2 and #3. Check the "HCV-only" box on the

Registration Page. Edit and update the consent status, and choose "consented to the study" (or other appropriate status) and enter the date of consent in the field provided.

For Waiver of Consent subjects, check the "HCV-only" box on the Subject Dialog box. Enter the consent status and choose "waiver of consent" and today's date of consent in the field provided.

6.2.3. *A2ALL-Link* HCV eCRFs

eCRFs will show up on your tasks list for eligible subjects who are 3 years or more post-transplant. Only those eCRFs that are applicable to your subject will be displayed for you to complete.

All eligible subjects get the following eCRFs:

- HCV Study Subject Flow
- HCV Transplant Information
- HCV Study Information
- HCV Advanced Disease Assessment
- HCV Transient Elastography Report (if applicable)

6.2.3.1. HCV Study Subject Flow eCRF

- Will appear for all eligible subjects.
- First section (Questions A-1 to A-6) reconfirms eligibility. If you answer "yes" to any of these questions, the subject is not eligible and no HCV eCRFs should be completed. If subject is "HCV-only", you should go back to the subject consent dialog box and change the subject's consent status to "Entered by Mistake".
- If subject is otherwise eligible for Core, then s/he remains in the main study.
- Section B determines what eCRFs are expected based on the eligibility answers.

Subject Scenarios

1) If the answer to B1 = no (subject has died or was re-transplanted)
   The following eCRFs should be completed:
   - HCV Transplant Information
   - HCV Study Information
   - HCV Advanced Disease Assessment
   - Post-Txp Bx Results

   Those subjects from the continuing sites who fit into this category will have already been uploaded into *A2ALL-Link* and any existing data will have also been uploaded into the appropriate eCRFs.

   No Biopsy slides will be requested for Central Read for this subject population.

2) If B1 = yes (alive)
   B2 = yes (prior evidence of cirrhosis)
   B2-1 = Biopsy findings (source = Bx)
   The following eCRFs should be completed:
   - HCV Transplant Information

- HCV Study Information
- Post-Txp Bx Results
- HCV Advanced Disease Assessment

NOTE: Request slides to be cut from the first Biopsy with evidence of cirrhosis for Central Read, and also the preceding biopsy, which did not show cirrhosis.

3) If B1 = yes (alive)
B2 = yes (prior evidence of cirrhosis)
B2-1 = Clinical evidence (source = clinical)
The following eCRFs should be completed:
   - HCV Transplant Information
   - HCV Study Information
   - HCV Advanced Disease Assessment
   - Post-Txp Bx Results

4) If B1 = yes (alive)
B2 = no (no prior evidence of cirrhosis)
B3 = yes (had Bx within past 12 months)
The following eCRFs should be completed:
   - HCV Transplant Information
   - HCV Study Information
   - Post-Txp Bx Results
     - If Ishak Fibrosis score was not noted on previous Bx, then this will have to be re-read
   - HCV Advanced Disease Assessment

NOTE: If subject has a scheduled Biopsy within the next 3 months, the answer to "had Bx within past 12 months" should be answered NO. Make a note in the comment box of the previous biopsy date, and state the subject has a scheduled biopsy within the next 3 months.

And, request slides to be cut from the Biopsy for the Central Read.

5) If B1 = yes (alive)
B2 = no (no prior evidence of cirrhosis)
B3 = no (no Bx within past 12 months)
B4 = no (will not get $\geq$ 3 yr Bx)
The following eCRFs should be completed:
   - HCV Transplant Information
   - HCV Study Information
   - HCV Advanced Disease Assessment
   - HCV Transient Elastography Report (if available)

NOTE: Consent subject for collection of bio-samples (Amendment #3).

And, request slides to be cut from the most recent Biopsy, for the Central Read.

6) If B1 = yes (alive)
B2 = no (no prior evidence of cirrhosis)
B3 = no (no Bx within past 12 months)
B4 = yes (will get $\geq$ 3 yr Bx)

The following eCRFs should be completed:

- HCV Transplant Information
- HCV Study Information
- Post-Txp Bx Results
- HCV Advanced Disease Assessment
- HCV Transient Elastography Report (if available)

Collect biopsy for slides for Central Read, along with the bio-sample collection (Amendment #2).

6.2.3.2. Fibroscan

- Transient elastography or Fibroscan is available at 3 sites: UCSF, Toronto, and Northwestern.
- Elastography will be performed on subjects at those sites who:
  - Will not get a Bx due to consent or safety reasons
  - Do get a protocol Bx (paired elastography done within 90 days of the Bx to validate the use of Fibroscan to Dx cirrhosis)
- Elastography will NOT be performed on subjects who achieved SVR post-TXP.
- Complete the HCV Transient Elastography Report eCRF for subjects that undergo Fibroscan.

6.2.3.3. Liver Biopsy

All eligible subjects will be approached for liver Bx unless they have:

- Re-transplantation
- Clinical evidence of decompensated cirrhosis
- Cirrhosis documented on previous Bx
- Liver biopsy performed within the last 12 months, and do not have a clinical Bx scheduled within the next 3 months (see Line 956 above)
- Coagulopathy precluding a liver biopsy

Liver biopsies will be obtained by the transjugular or percutaneous route (per site practice and PI discretion). In addition to unstained slides additional slides will be stained with hematoxylin/eosin (H&E) and trichrome. The Ishak scoring system will be used for staging of fibrosis to remain consistent with the central reading of A2ALL-1 biopsies. Inflammation, necrosis, steatosis, steatohepatitis, and evidence of fibrosing cholestatic hepatitis C (pericellular/sinusoidal fibrosis, cholestasis) will be assessed by the central pathologist. Concurrent conditions including acute and chronic rejection and histologic evidence of biliary disease will be noted. The central pathologist will also assess biopsy adequacy by counting the number of complete portal triads present.

The central pathologist will also evaluate biopsy slides for those subjects who underwent a biopsy in the past 12 months if that biopsy is serving as the surrogate for the protocol biopsy.

Non-invasive assessment (transient elastography) of fibrosis will be made for patients who refuse a biopsy or cannot have a biopsy due to safety concerns at UCSF, Toronto or Northwestern, or centers who acquire transient elastography equipment in the future. In addition, all patients who undergo biopsy at these centers will undergo transient elastography within 90 days of the liver biopsy for the purpose of validating liver stiffness with Ishak fibrosis score.

All subject's clinical data will be reviewed by members of the HCV Workgroup for evidence of having met the clinical end-points of cirrhosis or advanced disease.

The review will include assessment of the primary etiology of advanced disease (e.g., HCV disease or non-HCV factors including bile duct stricture, chronic rejection and vascular complications) or documentation of SVR after transplantation (based on undetectable HCV RNA at least 6 months after end of treatment).

Retrospective data will be retrieved from all recipients, including those who are not biopsied because they are already deceased, have clinically decompensated cirrhosis, had been re-transplanted, refused biopsy, have cirrhosis on a previous biopsy, or have a documented post-transplant SVR. For deaths and re-transplants, the data up to the time of death or re-transplant will be collected.

Scheduling in *A2ALL-Link*

1) Go to the task list for the subject
2) Choose Post-TXP Year 3+ HCV Visit
3) Enter the appointment information and save

Bio-sample Collection

- Collected at time of Bx, with consent Amendment #2.
- Collected at any time (with or without a previous 12 month biopsy or a 3 year protocol biopsy) with consent Amendment #3.
    - 1 SST Tube
        - 10 serum aliquots
    - 2 CPT Tubes or if available 2 Green Top tubes
        - 4 plasma aliquots
    - 2 EDTA
        - Whole blood for Genetics Repository <u>if not previously collected</u> (use extra sample labels and check "Whole Blood Genetics")

Extra Slides for Central Read

- Link the slide labels in *A2ALL-Link*, 4 slides are needed:
    - 1 stained H&E
    - 1 stained Trichrome
    - 2 unstained
- There are two sets of slide labels: one set of labels are to be used for the Year 3+ Biopsies, and the other set will be used for the past HCV biopsies.
- Put subjects ID, date of Bx, and type of slide (H&E, etc.)
- **NOTE: Do not apply the labels to the stained slides until after staining is complete and slides are dry.**
- **Order HCV slide labels from jenya.abramovich@arborresearch.org**
    - **When ordering your slide labels, be sure to indicate which type of label you are requesting.**

Sending Liver Biopsy Slides for Central Readings

All slides are to be sent to the following address:

Oyedele Adeyi, MD, FCAP, FRCPC
University Health Network
Department of Pathology (Rm. 11E206)
200 Elizabeth Street
Toronto, ON M5G 2C4
Canada

For questions:

Phone: 416-340-3136
Fax: 416-340-5517
E-mail: oyedele.adeyi@uhn.ca

- Use plastic slide cassettes that hold 4-5 slides, place as many cassettes as the shipping package will hold. Any other safe method is also acceptable.
- Slide shipment began in December 2012, followed with another slide shipment in March 2013.
- The next slide shipment to Toronto is in September 2013, and additional slide shipments will be decided on a month to month basis by the HCV Workgroup.
- Any courier can be used to ship the slides.
- Review shipping manifest and complete the HCV Bx Slide shipping task in *A2ALL-Link* (see *A2ALL-Link* User Guide, Section 7.7)
  - Please note that when shipping to Toronto, a value is required for customs. This value should be entered as $0.50 per glass slide. Also, please fill out the appropriate Export Forms (the Commercial Invoice and the U.S. Certificate of Origin), which will be included with the International Air Bill that is placed on the outside of the box.
  - Make sure to sign and date the Certificate of Origin. Include within the package your site's account/billing number for your regular courier service so that the duties, taxes, and shipping charges can be charged to your site when Dr. Adeyi returns the slides to your center following study completion.
- The slides will be kept at Toronto until the study is over and then returned to each site for storage.

6.2.3.4. Post-Txp Bx Results eCRF

This should be filled out for **each** post-txp Bx that occurs on all recipients. Continuing sites will receive a spreadsheet from the DCC which will list previously recorded post-transplant biopsies on their "HCV-only" subjects which were recorded in the Cohort study database. Any un-recorded post-transplant biopsies should be recorded in A2ALL-*Link.* For the HCV Protocol Bx, choose "HCV Protocol" for question A2 and indicate the Bx route in question A3.

Biopsy Results

- Indicate the diagnoses and make sure the Ishak Score is recorded in question A4.

- For those sites not using the Ishak Score to indicate fibrosis stage, the following answer choices are available in question A4:
    - No cirrhosis – As determined by alternative scoring system (e.g., METAVIR, Ludwig, Knodell or Scheuer <4) or specific notation on the biopsy path report that there is no cirrhosis.
    - Cirrhosis – As determined by alternative scoring system (e.g., METAVIR, Ludwig, Knodell or Scheuer =4) or specific notation on the biopsy path report that cirrhosis is present.
    - Not available
- **NOTE: All subjects undergoing the protocol Bx should have "HCV" checked on question A4 of the Post-Txp Bx Results eCRF.**

6.2.3.5. HCV Transplant Information eCRF

- Complete for all eligible subjects.
- Former Cohort subjects will have some fields pre-populated if answered in the Cohort database.
- All questions in Sections A-C should be answered retrospectively for the subject's status at the time of transplantation.
- Section A collects BMI components, dialysis and HCC Dx.
- Section B collects info about the donor.
    - If LDLT and donor information is in Cohort, parts of this section will be pre-populated.
    - Cold and warm ischemic times are based on the donation surgery.
        - Cold ischemia: the time from cross clamp to the time out of ice
        - Warm ischemia: the time from out of ice to arterial reperfusion
- Section C collects lab value at the time of transplantation (pre-op).
- Section D asks for the immunosuppression info at 1 year post-transplant.

6.2.3.6. HCV Study Information eCRF

- Date of cirrhosis assessment
    - For subjects who underwent the protocol biopsy, enter date of biopsy.
    - If previous biopsy with documented cirrhosis, enter date of biopsy.
    - Alive without re-transplant, enter Advanced Disease Assessment eCRF completion date.
    - Alive with re-transplant, enter Re-transplant date.
    - Dead without re-transplant, enter date of death.
    - Dead with re-transplant, enter date of re-transplant.
        - **NOTE: Timeframe for chart review = date of transplant to date of cirrhosis assessment.**
- Section A Post-transplant Follow-up
    - Question A2 collects information about post-transplant HCV treatment and response.
    - Question A3 collects information about rejection episodes and treatment.
    - Question A4 collects information about CMV Viremia.
        - **NOTE: CMV Viremia is defined as positive CMV by PCR.**
    - Question A5 collects information about biliary complications.
- Section B Status at Assessment
    - Time of cirrhosis assessment = date entered in Section A1.
    - Information is collected on the subject's clinical status and immunosuppression regimen at the time of the assessment.

- Section C Labs
    - Collects lab values closest to the time of cirrhosis evaluation.

6.2.3.7. HCV Advanced Disease Assessment eCRF

- Question A1 = Date of advanced disease assessment which is the date you complete the eCRF.
- The rest of the eCRF asks you to document signs, symptoms, and lab values that point to advanced disease, and the dates they occurred.
- Questions A11 and A12 is the investigator's assessment of whether subject met criteria for having advanced liver disease due to recurrent HCV.
    - **NOTE: Make an anecdotal note to file for source documentation of the investigator assessment.**

6.3. Donor Pain Study

Primary Aim 6: To understand the history of pain management and to measure quality of care in pain control in living donors following partial hepatectomy.

6.3.1. Consent

Consent for this substudy is contained in the Core Study Donor Consent that was included in Amendment #2.

6.3.2. Study Population

- Inclusion Criteria
    - Adult living liver donors

- Exclusion Criteria
    - History of chronic pain
        - Chronic or intermittent pain lasting for at least three months requiring treatment with narcotic pain medication
    - History of narcotic use
        - Routine scheduled narcotic use for treatment of a pain disorder diagnosed and treated by a physician
    - Medically unstable at 48 hours post-donation surgery
    - Language barrier

6.3.3. General Information

The Donor Pain Survey Version 3.2 (**Appendix N**) is to be administered by the study coordinator to the prospective post-operative donor subjects **48 to 72 hours post-operatively**. While it is acceptable to administer the survey up to 72 hours after donation, the goal is to try to administer the survey as close to 48 hours post-op as possible.

Coordinators may choose to print the form and enter the subject's responses by hand, or load the fillable form on to a laptop and enter data directly onto the survey electronically.

The study team should give careful thought regarding a plan for survey administration if the window occurs on a weekend or holiday. Note it is permissible for other clinical personnel to administer the survey with appropriate

training (junior physicians, nursing staff, etc.). It is also permissible to administer the survey over the phone. Make sure these variations are duly noted in the subject's research file.

6.3.4. Sedation Score

Before administering the survey, assess the subject's Sedation Score utilizing the 0-4 point scale detailed on the pain survey:

- 0 = Fully Awake.
- 1 = Light sedation, largely aware of self/surroundings. Mildly sleepy.
- 2 = Moderate sedation, slightly aware of self/surrounds. Somnolent but easily aroused.
- 3 = Deeply sedated, unaware of self/surroundings.
- 4 = General anesthesia, patient is unconscious.

Record the score, date, and time in the fields provided. A subject who scores above "2" should not be given the survey. In that event, record the date, time, and sedation score and come back another time (within the window) when the subject is less sedated. Record the date and time of the second attempt and the new sedation score in the fields provided.

6.3.5. Type of Pain Management

Record all types of pain medication routes (Intravenous push, oral, IM, etc.) that have been administered to the subject the first 48 hours since the donation surgery.

NOTE: Do not give the name of the medication being administered, <u>ONLY the route of administration of the drug given.</u>

6.3.6. Survey Administration

- Read the cover letter to the subject.
- Obtain the subject's verbal permission to proceed with the survey administration.
- Enter the subject's A2ALL ID # on each page of the donor pain survey.
- Enter the date and time of the first attempt to do the survey.
- Read each question to the subject, and explain the boundaries of the scale.
- Record the subject's answers on the survey.
- For question P11: if the subject indicates use of non-medical methods of pain relief, check all that apply.
- If a subject asks for clarification of a question, you must just repeat the question to the subject.
- Don't forget to thank the subject!

6.3.7. Documentation

On the Donor Post-op eCRF at 1 Week form, answer question C1.

6.3.7.1. Paper Forms

- Sign and date the original paper form and scan it. Save the form as a PDF and name it using the site ID #, the donor's A2ALL subject ID #, the date the survey was administered, and your initials separated by an underscore (e.g., 310_ D1234_082312_PHC). Save it to a secure location in a folder where you will save all electronic versions of the completed surveys.
    - Make two folders, one for surveys not yet transmitted to the DCC, and the other for surveys that have been transmitted.
    - If you do not have access to a scanner, you may transcribe the subject's responses on to the electronic version of the fillable PDF. Follow the instructions above for file naming and storage conventions.
- If you filled the form out on paper originally, save it as a source document in the subject's research file.

6.3.7.2. Electronically Completed Forms

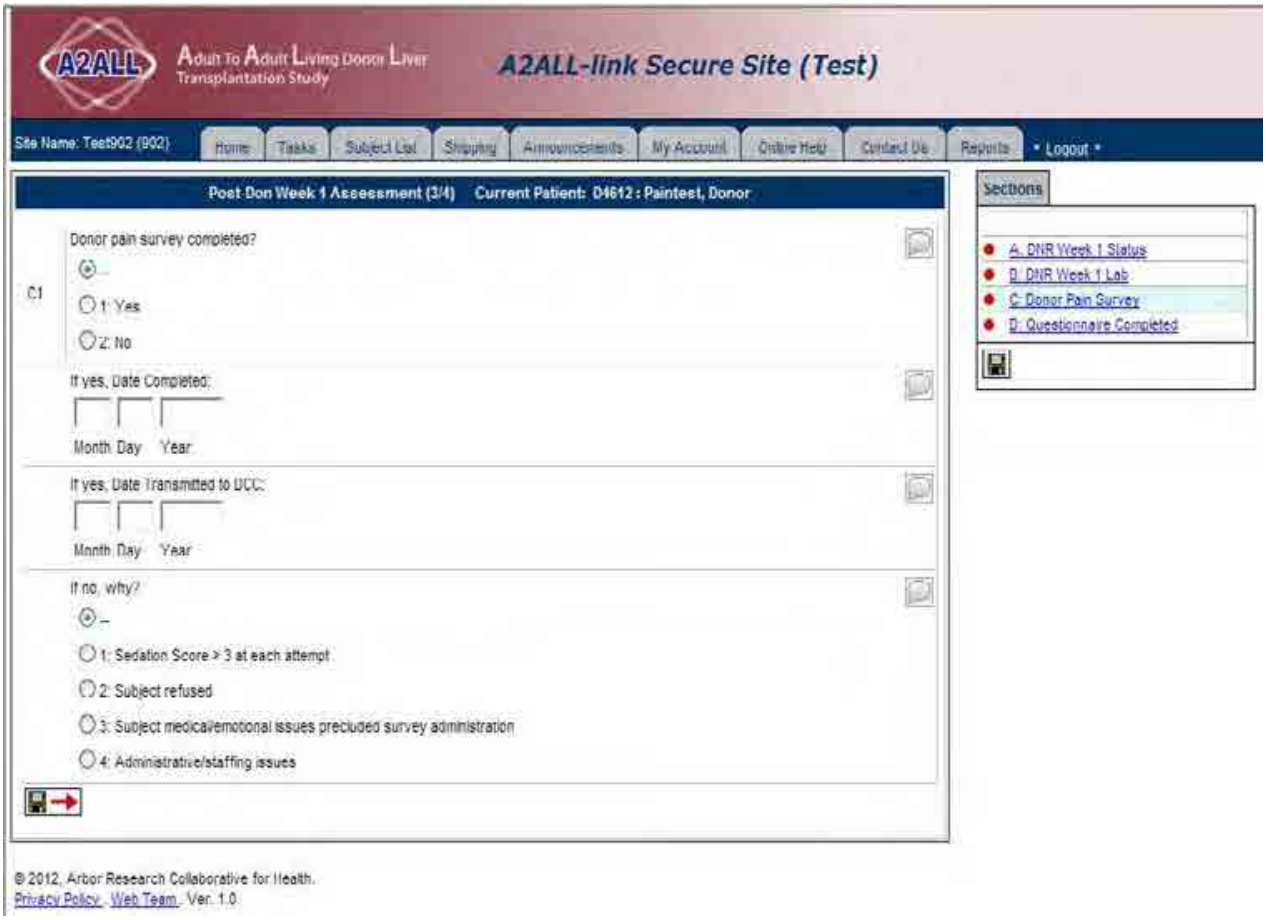
- If you filled out the survey electronically, save the form using the site ID #, donors A2ALL subject ID #, the date the survey was administered, and your initials separated by an underscore (e.g., 310_ D1234_082312_PHC). Save it to a secure location in a folder where you will save all electronically completed surveys.
    - As described above in section 6.3.7.1., make two folders, one for surveys not yet transmitted to the DCC, and the other for surveys that have been transmitted.

6.3.8. Transmission of Surveys to the DCC

- On the 15th of each month, transmit all forms not previously transmitted to the DCC by attaching them to one or more emails addressed to: a2all-painsurveys@umich.edu
- The DCC monitors will review the donor pain surveys for any irregularities.
- Should irregularities exist, the monitor will notify the study coordinator who conducted the survey with the subject and ask for the donor pain survey to be revised.
- After revisions are made by the study coordinator, the coordinator resends the revised donor pain survey to the DCC and indicates "revised" and the date change (if applicable) when re-naming the survey.
- If the 15th lands on the weekend, sites can transmit to the DCC the Friday before or the Monday after. This will also apply to holidays.
- You can access a list of untransmitted forms by going to the Reports tab in *A2ALL-Link* and selecting the Donor Pain Survey report. Convert it to Excel, choose "Auto filter" under the Data tab, and filter
    - Donor Pain Survey Completed = Yes
    - Date Transmitted to DCC = Blank
    - This will show you all of the completed surveys that have not been transmitted to the DCC. This should match all of the saved surveys in your "Not Transmitted" folder.
- After you send the completed surveys to the DCC, go to the Post-Don Week 1 Assessment eCRF and put the date sent in Section C1 and save the form.
- Move the transmitted surveys to your "Transmitted" folder.

6.3.9. Unable to Administer Survey

- If you are unable to administer the survey within the window, go to *A2ALL-Link* and complete Question C1 on the Post-Don Week 1 Assessment eCRF.
- Document the reason why the survey was not administered. Choices are:
  - Sedation score ≥3 at each attempt
  - Subject refused
  - Subject medical/emotional issues precluded survey administration
  - Administrative/staffing issues



7. ENROLLMENT CRITERIA

7.1. Core Protocol

- Recipients Inclusion Criteria:
  - Age 18 or older at the time of consent
  - Has had a living donor identified and accepted, and LDLT is planned
  - Informed consent obtained
  - Is listed for a single organ (liver) transplant
- Donors Inclusion Criteria:
  - Age 18 or older at the time of consent
  - Has undergone donor evaluation process, was accepted, and donation surgery is planned
  - Informed consent obtained

- Exclusion Criteria:
  - Prospective donors and recipients should not have undergone transplant/donation surgery prior to consent

7.2. Surgical Innovations (Pressure and Flow Measurement Study)

- Recipients Inclusion Criteria:
  - Age 18 or older at the time of consent
  - Has had a living donor identified and accepted, and LDLT is planned
  - Informed consent obtained
  - Is listed for single organ (liver) transplantation

7.3. HRQOL Study

- Inclusion Criteria:
  - All donors previously enrolled in A2ALL will be eligible if they are now >2 years post-donation, and donated in 2002 or later
  - All donors from the new A2ALL sites will also be eligible, if they have donated in 2002 or later, and are now >2 years post-donation
- Exclusion Criteria
  - Inability to comprehend spoken English

7.4. HCV Study

- Inclusion Criteria:
  - Continuing Centers
    - LDLT and DDLT recipients
    - Enrolled in Cohort or Core Gap (3 years post-transplant)
    - With evidence of HCV at transplant
    - Includes dead, lost to follow-up, and re-transplanted subjects (HCV-only subjects)
  - New Centers
    - LDLT and DDLT recipients
    - Transplanted between January 1998, and August 31, 2010
    - Had living donor evaluated
    - Had evidence of HCV at transplantation
    - Core Gap 3 years post-transplant
- Exclusion Criteria:
  - Refused Cohort study (continuing centers)
  - Documented SVR prior to transplant (non-detectable HCV RNA at least six months after end of treatment)
  - Co-infection with hepatitis B virus (HBsAg-positive) before transplant
  - Co-infection with HIV
  - Receipt of a graft from an HCV-infected donor
  - Died less than 90 days post-transplant
  - Re-transplanted less than 90 days post-transplant
  - Was one of the first 20 adult to adult LDLTs performed at the center

Surviving subjects who meet the inclusion criteria, and none of the exclusion criteria listed above will be approached for a liver biopsy unless they have one of the following conditions: re-transplantation, clinical evidence of decompensated cirrhosis, cirrhosis documented on previous biopsy, liver biopsy performed within the past 12 months, or coagulopathy precluding a liver biopsy. Those subjects who had a biopsy in the past 12

months or had cirrhosis on a previous biopsy will have the biopsies re-read by the A2ALL-2 central pathologist (Dr. Dele Adeyi, Toronto).

Inclusion of Subjects for the HCV sub-study of the Core Protocol: All recipients from the Cohort A2ALL-1 study (including former Retro subjects who consented to Cohort) with detectable HCV RNA after transplant will be eligible for inclusion. DDLT recipients from the new A2ALL sites (Toronto, Lahey, and Pitt) will be eligible if they had at least one potential donor present to the transplant center for evaluation, as per the original A2ALL-1 inclusion criteria.

NOTE: Subjects can still participate in the study if they refuse the biopsy. If subjects have had a biopsy within 1 year of enrollment, that biopsy should be read for data elements and entered onto the Post-Txp Bx Results eCRF. The pathology department should be notified and a request for the extra slides obtained.

If subjects are unwilling or unable to undergo a liver biopsy, the subject may be asked to undergo a procedure called "transient elastography". Toronto, UCSF, and NWU are the sites that will be using this non-invasive procedure in lieu of or in addition to (Toronto) having subjects undergo a liver biopsy.

Refer to Study Coordinator Training slides for HCV in Appendix J for further information.

8. POTENTIAL SUBJECTS FOR ENROLLMENT INTO THE CORE PROTOCOL

The following table identifies the cohorts of subjects who are eligible to be approached for enrollment into the Core Protocol and sub-studies:

Subject Type	Enroll into Core Protocol?	Enroll into HRQOL Sub-study?	HCV Study	Donor Pain Study	Existing Data Sources	Potential Data Entry Methods
Former A2ALL Subjects (continuing centers only)						
Full Cohort Donors Post-donation at the end of Cohort enrollment*	YES	YES	NO	NO	BioDBx***	Upload/New Data Entry
Full Cohort LDLT Recipients Post-transplant at the end of Cohort enrollment*†	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Full Cohort DDLT Recipients Post-transplant at the end of Cohort enrollment*†	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Cohort Lite Donors Post-donation at the end of Cohort enrollment* (donation occurred from 2002 – 2008)	YES	YES	NO	NO	BioDBx***	Upload/New Data Entry
Cohort Lite LDLT Recipients Post-transplant at the end of Cohort enrollment*†	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Cohort Lite DDLT Recipients Post-transplant at the end of Cohort enrollment*†	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Donors whose donation occurred in the Gap Era**	YES	NO	NO	NO	BioDBx***	Upload/New Data Entry
LDLT Recipients whose transplant occurred in the Gap Era**(must be three years post-transplant for the HCV Study)†	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
DDLT Recipients whose transplant occurred in the Gap Era**(must be three years post-transplant for the HCV Study)†	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry

Subject Type	Enroll into Core Protocol?	Enroll into HRQOL Sub-study?	HCV Study	Donor Pain Study	Existing Data Sources	Potential Data Entry Methods
New Subjects (all centers)						
Actual Donors shortly Pre-donation	YES	YES	NO	YES	NONE	New Data Entry
LDLT Recipients shortly Pre-transplant	YES	NO	NO	NO	NONE	New Data Entry
Donors whose donation occurred in the Gap Era**	YES	NO	NO	NO	NONE	Upload/New Data Entry
LDLT Recipients whose transplant occurred in the Gap Era**(must be three years post-transplant for the HCV Study)	YES	NO	YES	NO	NONE	Upload/New Data Entry
Donors that Donated Prior to the Gap Era** (new centers only)	NO	YES	NO	NO	NONE	Upload/New Data Entry
LDLT Recipients with HCV whose transplant occurred 1/1/1998 – 8/31/2010 AND had a living donor evaluated (must be three years post-transplant for the HCV Study), includes dead and re-transplanted subjects	NO	NO	YES	NO	NONE	Upload/New Data Entry
DDLT Recipients with HCV whose transplant occurred 1/1/1998 – 8/31/2010 AND had a living donor evaluated (must be three years post-transplant for the HCV Study), includes dead and re-transplanted subjects	NO	NO	YES	NO	NONE	Upload/New Data Entry

* End of Cohort Enrollment = August 31, 2009

** Gap Era = September 1, 2009 - Site Initiation for Core Protocol (will vary by site)

*** Data for former A2ALL subjects exists in BioDBx up through August 31, 2010. All subjects will be post-transplant/donation. Additional data for the time period September 1, 2010-Site Initiation for Core Protocol will have to be manually entered or uploaded via spreadsheet.

****Cohort Era = March 1, 2003 – Sept. 1, 2010

† HCV subjects who are dead, lost to follow-up, and re-transplanted subjects are included for the HCV sub study only, their data collected under a waiver of consent.

8.1. Strategies for Approaching Subjects

It is critical that site personnel put careful thought into how to maximize subject accrual and retention. Integration of research interventions into existing clinical flow will enhance acceptance and cooperation with colleagues, as well as minimizing wasted time and frustration for the subject.

Prior to implementation, study staff should meet together to discuss implementation strategies, thinking about the following questions:

- How do you find out when patients will be seen in clinic? How will you know if the clinic appointment has been rescheduled?
- How will you know who is being considered to receive or donate an LDLT?

- What kind of communication do you need to establish with your transplant/donor clinical team? Will the study coordinator need to attend meetings of this group?
- When is the last time the donor is in your facility after acceptance and before the operation hospitalization? What is the estimated interval?
- If there is a short time period (or none), then you will need to develop a plan to approach the subject prior to final acceptance. When is the optimal time?
    - In order to avoid the extra work of approaching and consenting subjects who will never go on to donate or have an LDLT, you should try to identify a time later in the evaluation process, after the subject has undergone and passed preliminary workup and is being seriously considered for donation. It has been suggested that at pre-op imaging may be a good time to approach the subject.
- How long do you think you will need to explain the study and obtain informed consent from donor and from recipient? Where will you do that? In clinic or in the research area?

9. BIO-SAMPLE COLLECTION AND OTHER STUDY-RELATED PROCEDURES

9.1. Blood & Tissue Collection for Genetics & Bio-sample Repositories – Overview

The sample processing associated with this protocol requires advanced skills. Prior to study implementation, PIs should meet with study staff and discuss the following questions:

- How will the samples be collected? Who will draw those samples? Do most of your patients have clinical labs drawn before they come to their clinic visit or on the day of the visit? If the latter, how can you coordinate clinical and research blood draw?
- Who will process the samples from their raw state to their component states for storage? Who will pick up the samples? Where do you pick them up from? Who will centrifuge, aliquot, and label the samples? Who will notify you that there are samples to pick up? How will you ensure that the samples are processed within the recommended time interval?
- How will you ensure that the samples are handled and labeled properly?
- If you are utilizing a research lab, have you met with them to discuss the study and the process for sample collection, processing, labeling, and storage? What about costs?
- Who will collect the intraoperative samples? Does the study coordinator need to be in the Operating Room (OR)? If the study coordinator is not going to the OR, who will make sure the samples will be collected, collected at the right time point, put into the right container, and labeled properly? Who will pick up the samples from the OR? Where will the samples be kept until picked up?
- Where will the samples be stored? When you are ready to ship out samples, how would you know where those samples are, how many samples you have, and which ones you need to ship out? Who has certification to ship bio-samples?

Information regarding bio-sample collection, processing and shipping is included in the MOO in **Appendix O**.

9.1.1. Donor Bio-sample Collection Schedule

Sample Type	Time Point						
	Pre-Donation	At Donation		Post Donation			
	Shortly Pre-Donation	Just Prior to Resection*	1° Post Resection**	Day 7	Month 1	Month 3	Year 1
Liver Bx - Biorepository		**3 CORE BX IN RNA LATER - FROZEN**	**3 CORE BX IN RNA LATER - FROZEN**				
Whole Blood – (DNA) Genetics Repository	**2 EDTA TUBES - AMBIENT†**						
Serum - Biorepository	**TEN 0.5ML ALIQUOTS - FROZEN**			**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**
Plasma - & Peripheral Cells Biorepository	**FOUR 0.5ML ALIQUOTS - FROZEN**				**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**
Nonviable cells (for future cell proteomics) - Biorepository	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**				**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**
Viable cells resuspended in 10% DMSO & 90% FCS for Flow Cytometry or other studies (such as stimulation) at a future date - Biorepository	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**				**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**
Whole Blood - RNA Extraction for future study	**2 PAXGENE TUBES - FROZEN**				**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**

*Biopsy is taken just prior to resection closest to the line of resection.

**Biopsy is taken from the remaining remnant 1 hour post resection or prior to closing.

†These tubes can be collected at any time during the study and only once (per Amendment #1 to the core protocol).

9.1.2. Recipient Bio-sample Collection Schedule

Sample Type	Time Point										
	Pre-TXP	At TXP		Post TXP							
	Shortly Pre-TXP	Back Table	1° Post Reperfusion	Day 7	Week 2	Month 1	Month 3	Year 1	Year 2	Year 3	Year 4
Liver Bx - Biorepository		**3 CORE BX IN RNA LATER - FROZEN ***	**3 CORE BX IN RNA LATER - FROZEN ****							**HCV-only subject********	
Whole Blood – (DNA) Genetics Repository	**2 EDTA TUBES - AMBIENT †**										
Serum - Biorepository	**TEN 0.5ML ALIQUOTS - FROZEN**			**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**
Plasma - - & Peripheral Cells Biorepository	**FOUR 0.5ML ALIQUOTS - FROZEN**					**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**	**HCV Plasma only**	
Nonviable cells (for future cell proteomics) - Biorepository	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**					**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**		
Viable cells resuspended in 10% DMSO & 90% FCS for Flow Cytometry or other studies (such as stimulation) at a future date - Biorepository	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**					**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**		
Whole Blood - RNA Extraction for future study	**2 PAXGENE TUBES - FROZEN**					**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**		

*Biopsy is taken from the donated graft while on the back table prior to implanting into recipient.
**Biopsy is taken from the donated graft after reperfusion is complete.
***All subsequent annual visits collect the same bio-samples.
****HCV RCP only; Bx performed if no clinical Bx was performed at this time point
†These tubes can be collected at any time during the study and only once (per Amendment #1 to the core protocol).

Any whole blood genetic samples previuosly collected (prior to repository initiation, May 2012) should be discarded at each site. Site is responsible for maintaining a list of those discarded samples.

The number and types of tubes needed for each subject at each visit are as follows:

- EDTA Tube (contains 3.6 mg K_2 EDTA (1.8 mg K_2 EDTA per ml) 2.0 ml draw; 100 tubes (38.96) @ $0.38 per tube. You need 2 tubes per subject for a **one time collection.**
- Serum Separator Tube (SST) (8.5ml * 4.5ml serum): 100 tubes ($53.44) @ $0.53 per tube; 1000 tubes ($487.13) @ $0.49 per tube
- Cell Preparation Tube (CPT) (8ml): 60 tubes ($522.75) @ $8.71 per tube (note that you will need 2 of these per subject per time-point) containing sodium heparin
- PaxGene: (2.5 ml)100 tubes ($798.21) @ $7.98 per tube (note that you will need 2 of these per subject per time-point)
- Prices above are taken from the Vendor VWR International. Their toll free number is 1-800-932-5000, web site VWR.com

9.2. Blood & Tissue Sample Collection, Processing, Storage, Packing, and Shipping

All sample processing is to be done under sterile conditions and in a certifed Bio-safety cabinet (TC hood).

The collection window for bio-samples is the same as the lab tests:

- The window for bio-samples to be collected at Weeks 1 and 2 is +/- 2 days from the actual date the visit occurred.
- The window for bio-samples to be collected at the monthly visits is +/- 7 days from the actual date the visit occurred.
- The window for bio-samples to be collected at the yearly visits is +/- 1 month from the actual date the visit occurred.

For procedures requiring washing of cells, sites should use sterile PBS that is Ca^{++} and Mg^{++} free.

1) **Ethylene diamene tetra-acetate (EDTA) Tubes – Whole Blood:** Collect 2 tubes (6ml suggested size)for storage of genetic material. These tubes can be collected at any time during the study and only once (per Amendment #1 to the core protocol).
    - Draw each tube to capacity.
    - Gently invert 8-10 times to mix solution with blood.
    - DO NOT CENTRIFUGE.
    - Tubes are shipped ambiently within 48 hours ofcollection.
    - For those specimens collected on Friday, invert 8-10 times, keep refrigerated at 4ºC over the weekend,and ship out on Monday.
    - No Saturday Deliveries are Allowed.

EDTA Tube

2) **Serum Separator Tube (SST) – Serum:** The tubes are coated with silicone and micronized silica particles to accelerate clotting with a gel plug to separate the clot from the serum. A silicone coating reduces adherence of red cells to tube walls. The silica coating can sometimes cause the inner tube wall to appear cloudy and/or filmy. This cloudy appearance does not make the tubes unacceptable for use.
    - Draw to capacity.
    - Gently invert 8 - 10 times to mix blood and facilitate the start of clotting.
    - Stand tube upright in rack allowing blood to clot for 30 minutes. (Longer than 45 minutes may cause hemolysis and glycolysis to take place.)
    - Centrifuge for 10 minutes, at 1500 to 1800 RCF. The gel in the tube should form a complete barrier between the serum and red cells.
    - Label 10 cryovials.
    - Aliquot 0.5ml per cryovial.
    - Freeze in –20°C freezer until shipping.
    - Ship on dry ice using the shipping containers supplied by the repository.

SST

PaxGene Tube

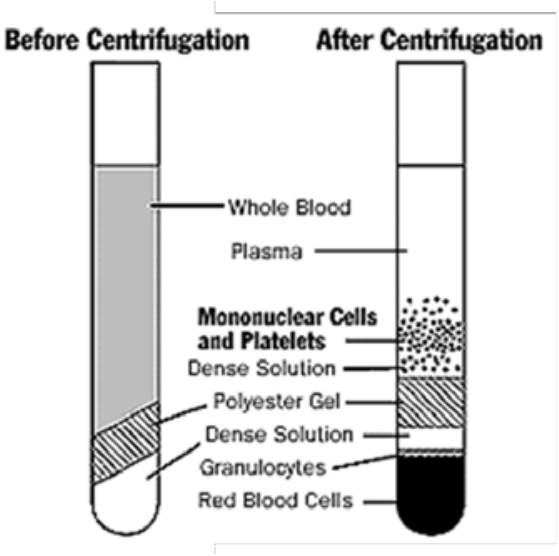
3) **PaxGene Tube:** Yields Whole Blood for future RNA extraction (draw prior to CPT Blue/Black tube).
    - Draw 2.5 ml of blood by venipuncture (do not use a syringe).
    - Invert the tube 10 times immediately after draw; do not shake.

- DO NOT CENTRIFUGE
- Repeat with the 2nd PaxGene tube.
- Freeze at –20°C upright in a wire or plastic rack (freezing in styrofoam may cause the tubes to crack) for 24 hours then transfer to a -80°C freezer until shipping.
- Ship on dry ice using the shipping containers supplied by the repository.

4) **Cell Preparation Tube (CPT):** Yields plasma and viable and nonviable peripheral blood cells. You will need to draw 2 CPT tubes (containing sodium heparin) at each designated time point.

CPT Tube

- Draw 8 ml of blood by venipuncture (do not use a syringe) into each CPT tube.
- Invert the tube 10 times **<u>immediately</u>** after draw, do not shake, and keep at room temperature.
- The CPT tube must be centrifuged within 2 hours from the time of the blood draw in a centrifuge with a swing-out bucket rotor for 20 minutes, room temperature at 1700 RCF (relative centrifugal force).
    - The centrifugation process will cause the plasma to separate from the mononuclear cells and platelets (see figure below).



5) **Plasma Aliquots:** after centrifugation, using a transfer pipette, carefully aliquot approximately 0.5ml of clear plasma from the uppermost layer into 4 cryovials, avoid disturbing the whitish cell layer, attach one barcode label to each vial, and freeze at –20°C.

6) **Collecting non-viable cells from CPT tube #1:**
- Recap the tube with the stopper and invert the tube 10 times.
- Pour off the cell/plasma mixture into the 15 ml blue cap tube.
- Add PBS (phosphate buffered saline) to bring the volume to 15 ml.
- Cap tube, mix cells by inverting tube 5 times.
- Centrifuge for 15 minutes, room temperature at 300 RCF.
- Aspirate as much supernatant as possible without disturbing the cell pellet, leaving a few microliters of supernatant with the cell pellet.
- Resuspend the pellet by <u>gently</u> vortexing or tapping tube with finger.

- Add PBS to bring volume to 10 ml.
- Cap tube, mix cells by inverting 5 times.
- Centrifuge for 10 minutes, room temperature at 300 RCF.
- Aspirate as much supernatant without disturbing the cell pellet, leaving a few microliters of supernatant with the cell pellet.
- **Quickly** resuspend the pellet by gently vortexing or tapping tube with finger.
- **Immediately** add 1.5 ml of RNALater to the cells (for more detailed information about RNALater, please refer to **Appendix P**).
- Resuspend and then transfer 0.5ml of the suspension into 3 barcode-labeled cryovials.
- Store in the freezer at –20°C.

7) **Collecting viable cells from CPT tube #2:**
   - **This procedure requires a freezing medium consisting of Fetal Bovine Serum (FBS) (that has been heat inactivated at 56°C for 30 minutes) and Dimethyl sulfoxide (DMSO).**
     - **DMSO must be fresh and sterility maintained. DMSO is stable at room temp for 6 months once opened.**
   - **DMSO must be chilled (on ice) prior to adding to cells.**..
   - Once the plasma layer has been removed, using a transfer pipette, remove the next layer (called buffy coat, appears beige in color) and place in a 15 ml conical tube. Add PBS to the tube slowly to bring the volume to 15 mls.
   - Mix the cells by gently inverting the tube 5 times.
   - Centrifuge for 15 minutes, room temperature at 300 RCF.
   - Aspirate as much of the supernatant as possible (use a transfer pipette) without disturbing the cell pellet. Leaving a few mls of the supernatant (wash buffer) is ok.
   - Re-suspend the pellet by GENTLY vortexing or tapping with your finger. Add PBS to bring the volume to 10 mls.
   - Cap tube, mix cells by inverting 5 times.
   - Centrifuge 10 minutes, room temperature at 300 RCF.
   - Aspirate as much of the supernatant as possible (use a transfer pipette) without disturbing the cell pellet.
   - Re-suspend the pellet with a volume of cold 90% FBS/10% DMSO to make a cell concentration of 1.5-2.0x 10^6cells/ml. Re-suspend the cells by tapping the tube gently with your finger until no clumps are visible. Do not vortex or pipette as this will damage the cells. Place the cell suspension on ice for 5 minutes to be sure the cells are cold.
   - Aliquot 1.0 ml of the cell suspension into 3 barcode-labeled cryovials.
   - Cryovials should be stored in liquid nitrogen. If liquid nitrogen is not available, cryovials can be stored in a -60°C to -90°C freezer.
   - Cryovials can be shipped on dry ice.

8) **Liver Biopsy Tissue Collection:** At the times outlined in the protocol, the surgeon should collect one core biopsy.
   - Prior to biopsy collection, prepare 3 cryovials (three for each biopsy= 6 cryovials) with RNALater and label them. RNALater information can be found in **Appendix O**.

- The donor biopsy collected prior to re-section is taken close to the line of re-section. The second donor biopsy is taken from the remnant liver in the donor an hour post-resection or just prior to closing if less than an hour.
- The first recipient biopsy is taken when the donated graft is on the back table. The second recipient biopsy is taken from the transplanted graft after reperfusion (venous and arterial).
- Using sterile technique, the core biopsies should be divided into 3 equal segments.
- Transfer each segment into a prepared (containing 1.5 ml RNALater) cryovial.
  Freeze in –20°C until shipment.

9.3. Imaging Studies

1) **Donors** – a Computerized Tomography (CT)/Magnetic Resonance Imaging (MRI) of the liver and spleen performed at evaluation, and 3 months post-donation to establish baseline and to assess regeneration. Variables include liver and spleen volumes.
2) **Recipients** – a CT/MRI of the liver and spleen performed at evaluation and 3 months post-TXP to establish baseline and to assess regeneration. Variables include liver and spleen volumes.
3) **As of September 10, 2012, it was decided by the Surgical Innovations Workgroup to discontinue gathering pre and post-transplant imaging study information on Gap recipients.**
4) **If measurements of spleen volumes are not part of standard of care, indicate a note in the comment in the comment text box on the eCRF to reflect this information.**
5) **Sites are encouraged to work closely with their Radiology Department to have CT/MRIs read for liver and spleen volume as part of pre-donation/transplant work-up and post-transplant/donation follow-up.**

9.4. Hepatic Flow Measurements

Equipment: Utilizing a vascular probe attached to the Transonic HT322 Flow-meter, pressure and blood flow rates through pertinent vascular structures will be measured intra-operatively in recipient subjects.

9.4.1. Equipment

Each site obtained the necessary equipment, consisting of 8 vascular probes and the flow-meter, from Transonic prior to the study's start. For questions or concerns about the products, please contact Transonic Systems, Inc., 34 Dutch Mill Rd., Ithaca, NY 14850, Telephone: 607-257-5300, URL: www.transonic.com.

9.4.2. Methods & Schedule

As of April 17, 2012, the A2ALL Steering Committee voted to stop collecting the pressure and flow measurements as well as the CVP and MAP readings in all donor subjects.

We'll be measuring the pressure and flows of the recipients only.

1) **Recipients:** Baseline measurements will be obtained of the portal and hepatic arterial flow and portal pressure, and will be repeated after the graft is

in place, and following any flow modulation procedures. To obtain baseline measurements, arterial and portal probes are applied after the proper hepatic artery and the common portal vein have been exposed in the course of the dissection. Please note that if the proper hepatic artery is not normally exposed in the dissection, or multiple arteries are present, the arterial measurements will be omitted and so indicated on the case report form, although the portal flow should be measured. The probes are selected, applied to the vessels, and arterial and portal flow measurements are obtained as described for the donor. If possible, once the measurements have been obtained, keep the probes connected to the flow-meter to avoid an extra use since each connection of the probe to the meter counts as a separate use. After the initial pressure measurement, a vascular clamp is placed proximal to the needle on the portal vein in order to measure the distal portal vein pressure and determine the gradient.

If a flow modulation is performed prior to removing the native liver, the measurements should be repeated. After the new liver is in place, the pressure and flow measurements are taken again. Flow probes are placed in the vessel at an appropriate location so that the diameter of the vessel at the site of the measurement assures optimal fit of the probe. If one or more flow modulations are performed, the measurements are repeated after each modulation. The case report form is designed to accommodate all these steps. If a measurement is not obtained for any reason, indicate this on the intraoperative worksheet. A space for comments is available to clarify any relevant observations.

Note: If there are two or more portal veins present, take readings on all vessels, add the readings and enter the sum into *A2ALL-Link*. Be sure to include a comment on the number of portal veins present.

Strips from the flow-meter should include the subject's ID number, name, and the type of vessel and the occurrence of the reading (i.e., native liver, prior to reperfusion, after modulation…). The original strips should be stapled to the intra-op worksheet. A copy of the flow-meter strip should also be placed in the subject's research file.

2) **Postoperative ultrasound measurement of portal vein flow:** Although a variety of potential measurements are reported on the postoperative ultrasound, the most relevant and reproducible measurement is the peak systolic velocity of the main portal vein. This number should be recorded on the 1 week post-transplant case report form.

9.5. Packing & Shipping Genetics and Bio-samples

- All labels are provided by the DCC by time-point and subject class. Keep the individual label sets separate.
- Keep all "unused" labels in the subject's research binder.
- If labels are found to be defective, notify jenya.abramovich@arborresearch.org to send more labels (be specific of timeframes).
- Send defective labels to Jenya through the postal service who will return them to the manufacturer.
- Specimens are to be inserted in labeled vials.
- Please use the label that is appropriate for the sample.
- Apply the label lengthwise along the vial.

- Remove all other subject identifiers from the vial.
- Update *A2ALL-Link* as soon as samples are obtained.
- **All frozen specimens should be sent to the NIDDK Bio-sample Repository with the monthly shipment**

9.5.1. A2ALL Core DNA Lab (Fisher BioServices) and Sample Handling

Fisher BioServices has contracted with the A2ALL study to extract DNA from whole blood, aliquot it, and send it to the NIDDK Bio-sample Repository (Thermofisher) for storage. All shipping materials will be provided by the Core DNA Lab. See **Appendix O** for shipping assembly instructions.

Genetic Bio-sample Collection

All whole blood samples will be sent to Thermofisher (division of Fisher BioServices) for DNA extraction, they will be aliquotted and returned to the Bio-sample Repository for storage. Two EDTA tubes are drawn at the time of enrollment for prospective subjects or, at the next study assessment for those subjects who did not have whole blood collected at the time of enrollment. Those former A2ALL subjects who did not have whole blood drawn in the previous A2ALL study will have this drawn at their next study assessment.

For those specimens drawn on prospective subjects not having whole blood collected at enrollment, or those former A2ALL subjects who did not have whole blood drawn previously, the labels to be used are the "extra labels" available on the sample page for the present study visit. Be sure all subject PHI has been removed from the blood collection tubes prior to applying the study specific labels.

Genetic specimens are shipped within 24 to 48 hours after collection and are shipped ambiently. Avoid shipping genetic specimens after Wednesday of each week.

Refer to Thermofisher's Holiday Schedule as their repository will be closed on those holidays, and will not be able to accept genetic shipments.

All genetic bio-sample shipping materials will be provided by the repository. This shipping kit includes:

- Cardboard box that should be used to ship the samples (EDTA tubes). See **Appendix O** for shipping assembly instructions.
- Small Styrofoam box.
- Two plastic (95kPa) specimen transport bags with an absorbent packet for 4 blood collection tubes each.
- Two polar packs.
- Instructions for shipping.
- FedEx Airbill as well as appropriate shipping stickers.
- Thermofisher Repository Shipping address:

Fisher BioServices
Attn. Laboratory Dept.
14665 Rothgeb Drive
Rockville, MD 20850

You must order your shipping supplies on-line through the following address: https://www.fisherbio.com/Client/BSDWeb/NIDDK_A2ALL/Login.asp

Fisher BioServices highly encourages sites to order shipping kits well in advance of need. In addition, please order kits in bulk if possible (avoid ordering 1 kit at a time).

NOTE: Please remember to include the FDA # in the FedEx Airbill to expedite the shipping process.

If you have problems with the supply order site, contact the following individual:

Daniel Forero
daniel.forero@thermofisher.com
Project Manager
Telephone: 301-315-8515
Fax: 301-294-4024

For information about the annual quality control process, refer to **Appendix Q**.

9.5.2. NIDDK Bio-sample Repository (Thermofisher) and Sample Handling

All samples, except the whole blood earmarked for DNA extraction at the DNA Core Lab, are shipped to the NIDDK Bio-sample Repository. All shipping materials will be provided by the repository. Each shipping kit consists of:

- Cardboard boxes that should be used to ship the samples (cryovials and PaxGene Tubes). See **Appendix O** for shipping assembly instructions.
- Large Styrofoam box
- 3 81-well cardboard vial boxes(cryovials), 1 49-well cardboard larger tube box (PaxGene)
- Instructions for shipping
- FedEx Airbill
- NIDDK Bio-sample Repository Shipping Address:

  Fisher BioServices
  20301 Century Blvd.
  Bldg. 6, Suite 400
  Germantown, MD 20874

To order shipping kits for blood and tissue specimens (other than genetics), sites are to request by email only to: Bio-NIDDKrepository@thermofisher.com

The DCC will provide each site with the following supplies:

- 2 ml cryovials for the aliquots
- Bar-coded shipping labels for the vials (one set for each subject)
- To order supplies from the DCC contact Jenya Abramovich (jenya.abramovich@arborresearch.org).

The following site identifying numbers are used in conjunction with repository communication.

Returning Centers		New Centers	
Columbia	310	Lahey	840
NWU	311	Pitt	841
Penn	312	Toronto	842
Colorado	313		
UCSF	315		
VCU	318		

Sites will ship to the repository based on the following schedule:

1st Monday of every month	Penn and Pitt
2nd Monday of every month	UCSF and Lahey
3rd Monday of every month	Columbia and VCU
4th Monday of every month	Toronto, NWU, and Colorado

Shipments are accompanied by a printed manifest to be utilized by the repository to confirm presence of all specimens in the shipment. An electronic copy of the manifest is also sent to the repository. Any discrepancies noted by the repository will be sent to the DCC for follow-up with each site.

Sites should adhere to the above schedule. If a holiday falls on the Monday, when the site is to ship, then the site should send the shipment the following day. Do not send shipments to the repository on a Thursday or Friday. Sites should notify the DCC Monitors (prior to shipping) if they have a situation where they need to send a shipment a week earlier or later. Sites will resume their shipment schedule with the next shipment.

10. SHIPPING OF BIO-SAMPLES THROUGH *A2ALL-Link*

You must ship all bio-samples to the repository on a monthly basis, even if you only have a few samples. For specific instruction for creating a shipping manifest and notification to the repository and DCC on the day of shipping see **Appendix R** *A2ALL-Link* User Guide v1.8.

11. LABORATORY TESTS

The Core Protocol calls for the collection of laboratory tests in order to provide clinical data to support use of the bio-samples in future research. Often the lab tests required by the protocol are also part of standard clinical care for people with liver disease and living donors. Do not enter duplicate laboratory results. If the laboratory tests were not performed, check not done for each laboratory test. If 7 or more days have elapsed between recipient enrollment, and the actual transplant surgery, laboratory tests should be run, rather than entering the same results from the prior tests. **When subjects are hospitalized at the time of an assessment the laboratory tests performed at 8:00 AM are to be entered.** The window for laboratory results collected at Weeks 1 and 2 is +/- 2 days from the actual date the visit occurred.

The window for monthly labs is +/- 7 days from the actual date the visit occurred.

The window for yearly labs is +/- 1 month from the actual date the visit occurred.

11.1.1. Schedule of Laboratory Tests – Donors

Event	Time Point									
	Pre-Donation	At Donation								
	Shortly Pre-Donation*	Just Prior to Resection	1° Post Resection	Week 1	Month 1	Month 3	Year 1	Year 2	Year 3	Year 4 and annually
LFTs	X			X	X	X	X	X	X	X
CBC	X			X	X	X	X	X	X	X
PT/INR	X			X	X	X	X	X	X	X
Bun	X			X	X					
Creatinine	X			X	X					

*Samples can be collected once the subject has received general anesthesia.

1) **Liver Function Tests (LFTs) include:**
   - Aspartate Aminotransferase (AST)
   - Alanine Aminotransferase (ALT)
   - Alkaline Phosphatase (ALK)
   - Albumin
   - Total Bilirubin
   - Blood Urea Nitrogen (BUN)
   - Serum Creatinine
   - Prothrombin Time (PT)/International Normalized Ratio (INR)

2) **Complete Blood Count (CBC) includes:**
   - White Blood Count (WBC)
   - Hemoglobin (Hgb)
   - Platelet Count

11.1.2. Schedule of Laboratory Tests – Recipients

Event	Time Point										
	Pre-TXP	Post TXP									
	Shortly Pre-TXP*	Day 1	Day 2	Day 3	Days 4-6**	Day 7	Days 8-13**	Week 2	Month 1	Month 3	Month 12 and Annually
LFTs	X	X	X	X	X	X	X	X	X	X	X
CBC	X	X	X	X	X	X	X	X	X	X	X
PT/INR	X	X	X	X	X	X	X	X	X	X	X
Sodium	X	X	X	X	X	X	X	X	X		
BUN	X	X	X	X	X	X	X	X	X		
Creatinine	X	X	X	X	X	X	X	X	X	X	X
Encephalopathy Grade Assessment***		X	X	X	X	X	X	X	X		

*Samples can be collected once the subject receives general anesthesia.
**Laboratory results entered only if labs performed as standard of care.
***Encephalopathy grade is assessed daily, and entered into *A2ALL-Link* in the appropriate eCRFs.

1) **The encephalopathy grading scale is as follows:**
   - 0: None
   - 1: Subject intubated/sedated-unable to assess
   - 2: Grade 1 – Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction.

- 3: Grade 2 – Lethargy or apathy; minimal disorientation for the time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 – Somnolence to semi-stupor, but responsive to verbal stimuli; confusion; gross disorientation.
- 5: Grade 4 – Coma (unresponsive to verbal or noxious stimuli).
- 6: Subject is not in hospital – unable to assess.

Daily encephalopathy grading must be sourced.

Note: Please provide source documentation for the encephalopathy grades for each day subject evaluated. The document must be signed, and dated by the individual(s) grading the encephalopathy on a daily basis and filed in the subject's research file (see Appendix L for source document tool)

2) **Liver Function Tests (LFTs) include:**
- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Alkaline Phosphatase (ALK)
- Albumin
- Blood Urea Nitrogen (BUN)
- Total Bilirubin
- Serum Creatinine
- Serum Sodium
- Prothrombin Time (PT)/INR

3) **Complete Blood Count (CBC) includes:**
- White Blood Count (WBC)
- Hemoglobin (Hgb)
- Platelet Count

11.1.3. Laboratory Ranges

Sites will enter their laboratory's normal ranges for laboratory results collected in the Core Protocol into the *A2ALL-Link* database.

Laboratory ranges were selected for the Core Protocol based on the 5th and 95th percentile for the laboratory values collected at the corresponding time point and subject class in the Cohort study. The database will warn you twice that a value is out of range: once at point of entry and again when the eCRF is saved. To ensure you have reviewed the out of range laboratory results, enter a comment in the comment text box stating you have verified the out of range laboratory result. Below are tables detailing laboratory value ranges for recipients and donors.

Recipient Laboratory Ranges (USA)

Lab	Shortly Pre-txp	Pre-op	Days 1-7	Days 8-14	Month 1	Month 3	Month 12 and Annually
Serum Creatinine	.60-1.8	.6-2.1	.6-2.7	.6-2.3	.6-2.2	.6-2.0	.7-1.84
Serum Albumin	2.0-4.2	1.8-4.2	1.9-4.0	1.9-4.0	2.2-4.3	2.6-4.5	2.8-4.7
Total Bilirubin	.60-11.8	.8-20.7	1.0-15.4	.6-11.7	.4-5.1	.3-3.8	.3-3.2
INR	1.0-2.2	1.0-2.5	1.0-1.7	.9-1.6	.9-1.6	.9-1.8	.9-1.4
Serum AST	25-220	28-355	20-210.5	14.0-143	13.0-127	16-200	16-168
Serum ALT	18.0-177	17.0-289	44-456	22.0-306	11.0-193	13-251	13-180
Serum Alkaline Phosphatase (ALK)	67-526	57.0-518	49.0-328	62-515	64-585	53-640	57-566
Serum Sodium	127-142	127-142	129-143	130-142	132-143	133-143	135-143
Drain Output*	xxxxxx	xxxxxx	10-1000	10-1000	10-1000		

*Drain Output – if a drain is not present at any time post-transplant check “not done”.

Donor Laboratory Ranges (USA)

Lab	Pre-op	Week 1	Month 1	Month 3	Month 12
Serum ALT	12.0-70.0	42-279	16-85	13-65	11.0-53
Serum AST	15-46	30-147	19-62	17-54	14.0-43
Serum Alkaline Phosphatase (ALK)	37-99	48-185	59-271	51-163	40-123
Total Bilirubin	.3-1.4	.6-4.2	.3-1.3	.3-1.3	.4-1.3
BUN	6.0-19.0	3.0-16.0	5.0-17.0	6.0-19.0	7.0-21.1
Serum Creatinine	.6-1.2	.5-1.1	.58-1.10	.6-1.1	0.63-1.2
Serum Albumin	3.3-4.9	2.5-3.9	3.0-4.6	3.4-4.7	3.6-4.8
INR	.9-1.20	1.0-1.5	.9-1.2	0.9	.9-1.2
White Blood Count	4.4-12.4	4.7-14.1	4.1-10.7	1.2	4.3-9.55
Hemoglobin	11.2-16.5	9.0-14.3	9.9-15.0	4-9.4	11.6-16.5
Platelet Count	176-370	125-357	149-447	135.5-331.5	137-325

- Each day of the Week 1 and Week 2 assessments asks if a drain is present. If a drain is present, answer “yes”, and enter the amount of fluid measured over a 24 hour period.
- If a drain was present, and the fluid was not measured, check “not done”. If a drain was present but removed, indicate in the comment text box the day it was removed (Day 3 or Day 4, etc.).
- If a drain is not present answer “no”.
- If a drain is present and the output measured is 0 enter “0”.
- **Remember: drain output measurements must be sourced. We are only collecting output from abdominal drains (i.e., Jackson Pratt (JP) drains).**

12. ANNOTATED eCRFs

The annotated Core eCRFs are located in the MOO in **Appendix S**.

Refer to **Appendix T** for the annotated HCV eCRFs and **Appendix U** for the annotated HRQOL-only eCRFs. HRQOL-only eCRFs will only appear in *A2ALL-Link* for the new sites (Pitt, Lahey, and Toronto). Refer to the HRQOL-only Site Training Slides (**Appendix V**) for more information.

The most current annotated eCRFs are located on the A2ALL study website, under Master Documents/Annotated eCRFs as well as in *A2ALL-Link*, under On-Line Help.

NOTE: A "Not Done" check box has been added to the weight data fields as of 10/24/2012.

13. DATA MANAGEMENT

The DCC has a comprehensive security plan for A2ALL-2 Core Protocol study data. The security plan is summarized in **Appendix K**.

The DCC has a robust security plan that was prepared with extensive consultation, and has been approved by Health Resources and Services Administration (HRSA). The security plan is based on the Privacy Act, the Computer Security Act, and OMB Circular A-130.

13.1. Gathering Data

- Data should derive from source documents. Source documents are original documents (the first place the information was recorded) that serve as the "raw data" for a study. Source documents include patient progress notes, laboratory reports, electrocardiograms (EKGs), medication records, x-rays, hospital records, research clinic records, subject diaries, and recorded data from automated instruments.
- Data on race/ethnicity can be collected by asking the subject directly for the information. Write an anecdotal note to file of the conversation to use as a source document, and file in the subject's research file.
- Keep in mind: "If it is not written down, it did not happen."
- If you have questions about the meaning of a question or data element, you should contact the DCC monitors for the definition. The goal is to keep interpretation of data elements consistent so that data collected can be properly analyzed and interpreted.
- If you have questions about what a notation means on a chart, then you should contact your site PI for a definition and interpretation.

Data Entry in *A2ALL-Link* on Specific Subject Types

1) **Former A2ALL subjects:** When a question asks "since the last assessment", this refers to the last time point in the Cohort Study. The time point at which these former A2ALL subjects enter into the Core Protocol starts at the current time point in their post-transplant or post-donation experience. For example, if a subject was transplanted in 2005, and the last follow-up was a 5 year visit in 2010, this subject is entered into the Core Protocol at year 6. When determining hospitalizations, complications, and biopsies, the time starts after the last visit in the Cohort Study ("since the last assessment"). For those former A2ALL subjects, complication resolutions should be completed in the following way:

If the complication resolved during the Cohort era (i.e., prior to August 31, 2010), and the subject is now in Core, you can no longer enter the resolution date in BioDBx as of June 2013. If the complication resolved after the end of the Cohort era, and the subject is in Core, make a note to file with the complication type and the resolution date.

2) **Gap Subjects:** When enrolling Gap subjects, prospective data entry will begin at the time point the subject is enrolled into the Core Protocol. For example, a subject is 3 months post-transplant/post-donation; the 3 month assessment visit (eCRF) will be completed. The question "since the last assessment" on the eCRF used for assessing hospitalizations and complications refers to the time of transplant/donation. A review of the subject's medical chart for any complications and hospitalizations (including transplant/donation hospitalization) since transplant/donation will be conducted, and the data entered into the appropriate eCRF.

3) The **Recipient Study Entry Form** for **Prospective and Gap** subjects also is to be completed. Data for this form is captured as close to the subject's transplant or donation date as possible. Laboratory results should also be as close to this date as possible. Imaging studies are not collected for Gap subjects.

Data is not collected on Gap recipients who received a DDLT, unless they are eligible for the HCV sub-study.

4) **Completing the Complication eCRF: When completing the complication eCRF, remember to record the onset date which is defined as the first occurrence noted or at the discretion of the PI, usually involving some kind of treatment or other intervention. When recording the resolution of a complication, keep in mind, a complication is resolved either when there is positive evidence that it is resolved (e.g., ultrasound showing resolution of post-donation ascites) or the patient has become asymptomatic (e.g., DVT) at the decision of the PI. Recipients have a list of 49 study tracked complications, whereas the donors have 47. If the complication is not listed, it is not recorded. See Appendix W for definitions of the complications tracked in the Core study.**

5) **Completing the Hospitalization eCRF: Enter the date of admission, and the date of discharge. Remember those admissions <24 hours are not considered a hospital admission. The ICD 9 code(s) to be used define(s) the reason for the admission. More than one ICD 9 code can be entered into *A2ALL-Link*. Separate these with a comma.**

If the subject is spending time in the Post-Anesthesia Care Unit (PACU) following their transplant/donation surgery, or any other surgical intervention, please note that one day (24 hours or overnight in PACU) should correspond to one day in the Intensive Care Unit (ICU) when recording number of days in ICU for question A5 in the Hospitalization eCRF.

6) **If a particular data field does not have a "Not Done" box, enter a comment in the corresponding comment text box indicating the data was not collected or the procedure/laboratory test was not done.**

HCC Data Collection:

- For subjects with hepatocellular carcinoma (HCC), clinical information regarding tumor characteristics will be collected on the explant eCRF. The information collected will be entered into *A2ALL-Link* on the Explant eCRF. The Explant eCRF is only completed for those recipients with a pre-txp diagnosis of HCC (the HCC diagnosis has been checked on the RCP Study Entry Information eCRF), or those who have an incidental finding of HCC on the explant.
    - If the pre-diagnosis of HCC was not verified or incorrect from the explant pathology, report the answer on the RCP Study Entry Information eCRF will need to be changed to "no".
- Staging of HCC will utilize the tumor-nodes-metastases (TNM) scale. This scale is listed below and also included in the appropriate eCRFs.
    - Stage I = 1 nodule <1.9 cm
    - Stage II = 1 nodule 2.0-5.0 cm; 2 to 3 nodules all <3.0 cm
    - Stage III = 1 nodule >5.0 cm; 2 to 3 with any nodules > 3.0 cm
    - Stage IVA1 = >4 nodules of any size
    - Stage IVA2 = Stage II, III or IVA1 plus gross intrahepatic portal or hepatic vein involvement on imaging
    - Stage IVB = Lymph node or distant metastasis or extrahepatic portal or hepatic vein involvement
- **For Gap subjects who have HCC diagnosis checked on the RCP Study Entry eCRF, the Explant eCRF will be available for completion in *A2ALL-Link* and you will be required to complete the form. For those Gap subjects who had an incidental finding of HCC on their explant, notify the DCC to have the Explant eCRF uploaded into *A2ALL-Link* for the subject.**
- **Post-Transplant HCC Recurrence**
    - **For those subjects with HCC, who experience recurrence post-transplant, the recurrence is tracked as a complication. The start and stop date of the recurrence will be collected. The ICD 9 code for HCC is 155.0.**

Things to Remember

1) If a prospective recipient, who has been scheduled for a living donor receives a DDLT, this recipient and the matched donor (if consented to study) are out of the study. In *A2ALL-Link* enter these subjects as "removed from study-reached study endpoint" in the consent status box on the consent dialog page. All data collection stops for these subjects. If a prospective donor does not donate (recipient receives DDLT or becomes too ill for LDLT, or donor is ruled out), this subject will have also reached a study endpoint. Enter this donor as "removed from study-reached study endpoint: in the consent status box on the Subject Dialog page. All data collection stops.

2) **If a former A2ALL subject (recipient) was re-transplanted** prior to the Core protocol, this subject is not eligible for entry into the Core protocol. Enter the subject as "removed from study-reached study endpoint" in the consent status box on the consent dialog page. With approval of Amendment #2, this subject population is covered under a waiver of consent for collection of complication and hospital admission data. Review the subject's medical records from the last follow-up date in Cohort to the date of re-transplantation. Enter all complication and hospital admission data occurring in the period onto the Core eCRFs.

3) **If a former A2ALL subject** (recipient and/or donor) **died** prior to approach to consent for the Core protocol, enter the subject as "Approached Dead" into the consent status box in A2ALL-Link. Review the subject's medical records from the last follow-up date in Cohort to the date of death. Enter all complication and hospital admission data that occurred during this time, onto the Core eCRFs.

4) **If a Gap Era subject (continuing and new sites)** was not eligible for consent into the Core study due to death, re-transplant, or graft failure, these subjects should be entered into A2ALL-Link under a waiver of consent. Enter the subject as "Waiver of Consent" in the consent status box. Complication and hospital admission data should be reviewed from the time of transplant/donation, to the time of death, re-transplant, or graft failure. The appropriate eCRFs should be completed in *A2ALL-Link* (Complication and Hospitalization eCRFs). The subject dialog box should also be completed in *A2ALL-Link*.

5) If a prospective recipient is re-transplanted, this subject is out of the study. Enter this recipient as "removed from study-reached study endpoint" in the consent status box on the Subject Dialog page (contains PHI).Enter the information regarding the re-transplant. All data collection stops. The matching donor for this recipient (if enrolled) is still followed in the study.

6) Former Retrospective subjects are not eligible for the Core Protocol unless they were enrolled into the Cohort study as Cohort-Lite.

Intra-Operative Worksheets: The intra-operative worksheets for donors and recipient subjects can be found in **Appendix L** as well as on the A2ALL website under Master Documents. The worksheets are completed, signed, and dated by the surgeon performing the surgery within 24 hours of surgery completion. The worksheets must contain the subject ID #, date of surgery and subject name at the top of every page. Data from these worksheets is entered into *A2ALL-Link* on the Intraop eCRFs. You will be asked to verify entries on the worksheets where actual surgical details are required (type of procedure, hypotensive episodes of the donors, blood product use, and height and weight measurements). The tracings collected after each reading should be attached to the appropriate worksheet, be sure the subject ID # is recorded on the tracings. A copy should be made of the tracings in case the originals become separated from the worksheets.

If at any time the anatomy of the donor or the reconstruction of the recipient is not accurately depicted in the diagrams provided on the worksheet, choose the one that closely represents the anatomy or reconstruction type. Be sure to include a comment in the corresponding comment text box describing the actual anatomy or reconstruction type.

Small for Size Syndrome: The site PI assesses whether or not a recipient subject has experienced "small for size syndrome". The questions are asked on the Post-Txp Week 1 Assessment eCRF. To verify the site PI has made this assessment the DCC has provided a source document (Appendix L) which sites may choose to adopt locally. This document is to be completed, signed and dated by the site PI at the Week 1 assessment.

Documenting a Subject's Death:

- **If a subject is a former Cohort subject, and you discover they have died as you approached for consent use the "Approached-Dead" status.**
- **If the subject was consented to the Core study, and expired while in the study, use the "Dead" status.**
- **Death of a subject is noted on the subject dialog box. Enter the date of death and the cause of death if known. Also enter the status of the graft at the time of death if known.**
- **The consent status for deceased subjects is also updated, by clicking on "edit status" in the subject dialog box. When the consent history box opens, click on "update status", from the consent status list choose "dead" status and enter the Date of Status Change. In the Date of Status Change field, enter the date you discovered the subject's death. Do not enter the date of death into this field. Click, save, and close the Consent Status Update dialog box. Be sure to save prior to closing the window.**
- **Please inform the DCC of any donor deaths ASAP. Do not use the email functionality in the *A2ALL-Link* application for this purpose. Contact the Project Manager (peg.hill-callahan@arborresearch.org).**

13.2. Data Timeliness

- Confirmation that a scheduled visit (visit status) has occurred, and samples (sample status) were collected is required within 48 hours of the visit.
- All subject data should be entered into the database within three weeks of study assessments. Information on the number, and types of samples collected is required to be entered within one week from the time of the assessment.
- Serious adverse event information should be entered into the database within 24 hours of the site being informed of the event. Reports should be updated as soon as information becomes available.
- Do not mark an eCRF complete until the entire eCRF has been completed.

NOTE: These are the measurements for overall protocol adherence as reported on the DSMB site report cards.

13.3. Data Sources

- New Recipient and Donor Subject Records – laboratory results will be collected; exam, lab, and procedure data will be collected. Results from for-cause biopsies will be recorded for recipients, as well as imaging results for all subjects.
- *A2ALL-Link* Database – certain variables already collected in the A2ALL Cohort study will be uploaded into the *A2ALL-Link* database (demographic info, date of transplant, etc.).
- National Databases – periodically, the DCC plans to link to national databases such as the Scientific Registry of Transplant Recipients (SRTR) and SSDMF (Social Security Death Master File) to update information regarding subjects' vital and graft status.

13.4. *A2ALL-Link*

Sites will utilize the web-based *A2ALL-Link* program as the data entry nucleus for the A2ALL-2 Core Protocol studies. Briefly, *A2ALL-Link* is a highly flexible database

application that allows investigators to organize their research operations, and perform common actions on research data within a single database.

A2ALL-Link can be accessed through the A2ALL website at: http://nih-a2all.org/. A separate user ID and password is required to log into *A2ALL-Link*. Note that passwords are case-sensitive. In accordance with GCP guidelines, *A2ALL-Link* user IDs, and passwords must not be shared. New personnel requiring access to the study database should complete appropriate training with the DCC, and request a unique username and password from their site's primary coordinator.

Sites should disable names of personnel in A2ALL-Link when they have left their position in the study or institution.

13.4.1. Logging into *A2ALL-Link*

The *A2ALL-Link* data base may be accessed from the following websites:

The main A2ALL study page www.nih-a2all.org
Or https://secure.arborresearch.org/a2all.

Once you've successfully logged into the system, an announcement box will open. The announcement box will contain messages on any overdue expected study assessments, procedures, data entry, or bio-sample shipping.

13.4.2. Use of Protected Health Information (PHI)

The *A2ALL-Link* study database will only utilize PHI on one page, and will use unique study identification numbers on all other data entry pages. Available PHI from *A2ALL-Link* will be pre-populated into the *A2ALL-Link* database. The PHI will be encrypted, and visible via a de-encryption key available only to the site's authorized personnel. The DCC will not be able to view the encrypted data and will not have the key. Sites will only have access to their own data, and PHI will not be shared between sites. Data analysis files will be de-identified. At the earliest time possible, consistent with the completion of the project, the DCC will destroy data linkages that contain PHI.

Within *A2ALL-Link*, each site will be prompted to create a *Patient Name Key* when logging in for the first time. Once created, the key should be kept in a secure place. The DCC will not be able to help with name key recovery as the key is confidential to each site. The *Patient Name Key* is the same for all users at

one center and allows the *A2ALL-Link* user to access PHI. The key should only be communicated to site staff using *A2ALL-Link* for the A2ALL-2 Core Protocol studies.

Encrypted Subject List

13.4.3. Unencrypted Subject List

13.4.4. Subject List

The Subject List contains all eligible A2ALL Cohort subjects uploaded from *A2ALL-Link* from the original A2ALL sites. The former Cohort subjects will retain their Cohort study ID numbers (R#### for recipients and D#### for donors). Sites have the ability to add PHI to these subjects' *A2ALL-Link* records for future ease of search and study conduct.

If you consent a former Cohort subject who has not been uploaded into *A2ALL-Link*, contact the DCC through the *A2ALL-Link* help tab, and include the A2ALL subject ID #.

Sites will have the ability to add new donor and recipient subjects to *A2ALL-Link*.

All site subjects will be listed on several pages within the database. The subject list is searchable on a variety of parameters, including name and subject ID #.

Search by Subject Name – choose parameter, and enter search criteria in window and click "Go."

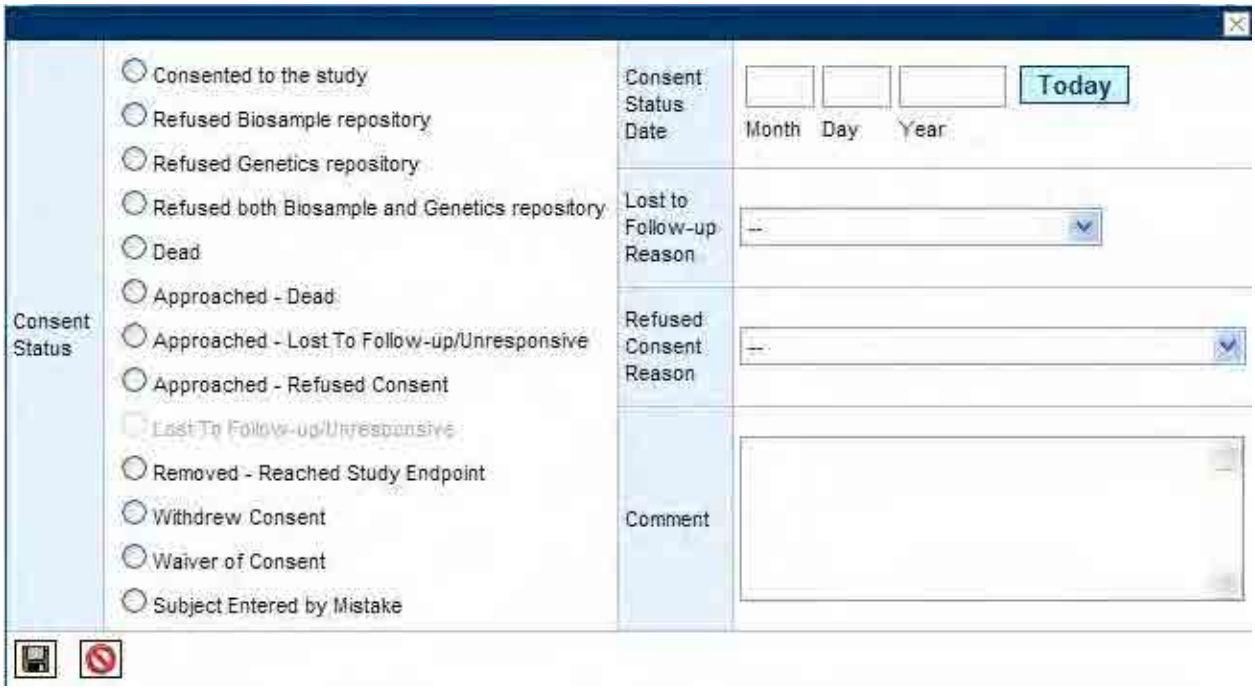
Search Results Display

13.4.5. Entering Consent Status for Subject

From the subject list, click on the subject ID # of the subject whose consent status is to be updated/changed. Choose to "Edit Consent Status." When the Consent History Dialog box opens, choose the appropriate consent status, and enter the date of consent. Clicking "NOW" defaults to the current date. All subjects (does not apply to former A2ALL subjects who are approached, and found to be dead) should have an original date of consent to the Core Protocol. For those subjects who are "HCV-only" and "HRQOL-only" check the appropriate box in the Subject Dialog page.

When updating the consent status (subject removed from study, subject expired, etc.), click on the subject ID # whose consent status is to be updated/changed. Choose to "Edit Consent Status". When the Consent History Dialog page opens, choose "Update Consent Status" (gray box). Choose the appropriate consent status, and enter the date of the consent status change.

To view the Consent History, click on "History" in your subject list of the subject chosen whose Consent History is to be viewed.



13.4.6. Adding a New Subject

From the subject list, click on "Add a new subject." The Subject Dialog page will open. Enter the new subject as a donor or recipient. Once subject class is designated, the system will generate a subject ID # for the new subject. The subject ID # will be either an "R" or "D" followed by a four-digit number code (e.g., R1890 or D1981). Enter the rest of the data in the appropriate fields on the page.

Link the subject to the proper member of the donor/recipient pair by clicking the "Link To" link and choosing the appropriate person.

Click the "save" icon when done.

NOTE: YOU WILL BE UNABLE TO ENTER PHI UNLESS YOU HAVE PREVIOUSLY ENTERED THE NAMEKEY. Click the "Namekey" link at the top of the Subject List to enter it after you have logged in.

13.4.7. Case Report Forms

The following list of data entry pages were created in *A2ALL-Link*.

- Subject Roster (Subject Dialog page) – contains subject PHI (encrypted and only visible at site level), blood type, date of surgery, relationship to recipient/donor, consent status, UNOS ID (PXID for recipients and Donor ID for Donors), date, cause of death if applicable and re-transplant information.
- RCP Study Entry form, which includes information about the subject's diagnosis, laboratory results prior to transplant as well as imaging studies.
- Intra Operative includes laboratory results on the day of the procedure, information on the surgical procedures as well as information for the surgical innovations aim of the protocol.
- Explant Form, collects information on HCC.

- Post-Donation or Post-Transplantation Assessment Forms, which include vital status, graft function, laboratory results, as well as bio-sample collection information.
- Hospitalizations
- Complications
- Serious Adverse Event (SAE) Report
- Protocol Deviation
- Post-transplant Biopsy Results, includes the HCV Biopsy, collects information on HCV recurrence, and rejection.
- HCV eCRFs: include the HCV Study Subject Flow, HCV Study Information, HCV Transplant Information, HCV Advanced Disease Assessment, and HCV Transient Elastography Report.

Electronic Case Report Forms (eCRFs) available for each subject can be accessed from the Subject List by clicking the CRF link in the CRF column. The Tasks list page will show a table listing eCRFs that are expected. The table shows a due date next to each expected eCRF. The due date is calculated based on date of the transplant surgery or donation surgery.

Once a visit is completed, you have 3 weeks to complete the appropriate eCRF, and 1 week to enter information on the number and types of samples collected. If these deadlines are not met, you will receive an overdue notice once you've logged in to *A2ALL-Link*.

13.4.8. Calendar Function for Appointment Scheduling

Once the transplant/donation surgery date is entered into the system, all future study assessment dates will be calculated, and placed on the calendar as "tentative." As the time draws closer for each tentative appointment, the system will remind you that the appointment needs to be "scheduled." The appointment's status is changed on the Tasks list. If the date of transplant or donation is incorrect, notify the DCC through the *A2ALL-Link* "help" button, include the subject ID #. Once a visit has been completed, change the visit status to "visit occurred". For Gap subjects those visits occurring prior to enrollment are changed to "visit occurred prior to site initiation". If a subject misses a visit, change the status to "missed".

NOTE: If the transplant is rescheduled for greater than 7 days after the 1st transplant date, when the date is changed, a pop-up window appears with the following information:

> Are you sure you want to change the transplant/donation date? This new date is >7 days after the previously scheduled date. Clicking "yes" will clear the information from the previous pre-txp visit event. It is not necessary to re-enter the Recipient Study Entry Form, but you will need to complete the following tasks:
>
> 1) Schedule the visit.
> 2) Link Barcode for pre-op labels, and collect pre-op samples. If genetic samples have been collected, they should not be collected again. The labels on the previously collected genetic samples should be re-labeled with new labels associated with the new visit.

3) If the genetic samples have already been shipped, notify the DCC using a2all-monitors@umich.edu who will give you further instructions.
4) Previously collected samples need to be discarded if they are still at your site. If the previously collected pre-op samples were shipped to the repository, please send a list of the samples shipped to the DCC.
    a. Site personnel can look at upcoming events by filtering the Tasks list by time interval (e.g., week, month, etc.). The Tasks list can also be filtered by subject ID #.
5) Once the time of a scheduled visit has occurred, the system requires that you enter information regarding whether the visit actually occurred, and whether or not samples were collected. You have 48 hours to confirm visit status and sample status completion.

Comments: Every eCRF field has comment functionality. The comment functionality should be used sparingly. To enter a comment, click on the callout balloon icon on the upper right corner of each field. The icon changes when a comment is added.

Event Driven Forms: Serious adverse event, protocol deviation, hospitalization, complication, and post-transplant biopsy results eCRFs must be added if an event occurs. On the eCRF page, click on "Serious Adverse Event" or "Protocol Deviation," then "Add New…" Complete the fields in the eCRF, and click the save icon. The new eCRF will appear on a list.

13.4.9. Data Queries and Management in *A2ALL-Link*

The *A2ALL-Link* electronic data entry system will have built-in data checks as part of study quality assurance. Protocol compliance will be assessed by monitoring the submission of data at required intervals. Data inconsistencies and discrepancy reports will be reviewed by a Clinical Monitor so that necessary queries can be generated, and sent to the transplant center study sites for verification and resolution.

Periodic requests may be generated for the submission of random source documents to assess the quality of data acquisition and data entry at each site. In addition, a Clinical Monitor will visit each site at least once to review source documents, monitor regulatory compliance, and assess protocol adherence.

In addition to source document verification, the Clinical Monitors and Program Analysts will produce reports from the *A2ALL-Link* system to look for inconsistencies in submitted data.

14. PROTOCOL COMPLIANCE

Compliance (in relation to trials) is defined as adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Please refer to the most recent version of the protocol to review eligibility criteria for each donor and recipient subject.

14.1. Visit Windows

Visit Windows for Recipient Post-Transplant Assessments (visit based on the date of transplant):

- TXP to Day 10 = Week 1
- Day 11 to Day 22 = Week 2
- Day 23 to Day 60 = Month 1
- Day 61 to Day 228 = Month 3
- Day 229 to18 mths-1day = Month 12
- 18 mths to 30 mths-1 day = Year 2
- 30 mths to 42 mths-1 day = Year 3
- 42 mths to 54 mths-1 day = Year 4

Visit Windows for Donor Post-Donation Assessments (visit based on the date of donation):

- Donation to Day 18 = Week 1
- Day 19 to Day 60 = Month 1
- Day 61 to Day 228 = Month 3
- Day 229 to 18 mths-1 day = Month 12
- 18 mths to 30 mths-1 day = Year 2
- 30 mths to 42 mths-1 day = Year 3
- 42 mths to 54 mths-1day = Year 4

14.2. Protocol Deviations

A protocol deviation is defined as a variation from the protocol-directed conduct of a clinical trial. Any noncompliance with the study protocol, Good Clinical Practice, or protocol-specific MOO requirement is considered a protocol deviation. All protocol deviations should be reported by adding and completing a Protocol Deviation eCRF in *A2ALL-Link* (see sample Protocol Deviation eCRF in **Appendix S**). Further information on protocol deviations can be found in ICH 4.5, Compliance with Protocol.

Complete questions A1 through A8 in *A2ALL-Link*. Save the eCRF, and then print the form. Have the PI review the deviation and complete questions A9 and A10. You may fax the completed and signed form to the DCC at (734) 665-2103, but please notify (e-mail) the site specific monitor prior to sending the document. A scanned copy of the document can also be emailed to a2all-monitors@umich.edu.

When it is received by the DCC, it will be reviewed and signed by Peg Hill-Callahan, Project Manager. The scanned document will then be returned to the site from the DCC by email to the study coordinator.

Protocol deviations are submitted to the site's IRB as per their IRB regulatory guidelines.

14.2.1. Major Protocol Deviations

A major protocol deviation includes a deviation which impacts one of the following:

- The inclusion and/or exclusion criteria
- Impacts the ability of the sponsor to evaluate the endpoints of the study
- A consent violation

14.2.2. Minor Protocol Deviations

A non-major protocol deviation (minor deviation) includes a deviation which includes noncompliance with the study protocol, GCP, or protocol-specific MOO requirement that does not meet the definition for a major deviation.

Below is a list of some of the Protocol Deviations (Major and Minor) the DCC will be tracking:

- Subject enrolled, but does not meet eligibility criteria.
- Non-adherence to study design.
- Loss of samples or data as per protocol schedule of events.
- Failure to obtain informed consent prior to initiation of study-related procedures.
- Falsifying research or medical records.
- Performing tests beyond professional scope.
- Working under an expired professional license/certificate.
- Breach of confidentiality.
- Improper or inadequate informed consent procedure.
- Other, specify:

Protocol deviation reports are to be submitted to your IRB per their reporting procedures. The response to the deviation reports are to be filed in the regulatory binder under major correspondence.

14.2.3. Study Termination and Completion

Subjects may be prematurely terminated from the study because of withdrawal of consent, failure to return (lost to follow-up), reaching an endpoint (surgery canceled or aborted, or recipient receives DDLT), or death. Every attempt will be made to follow subjects who prematurely terminate from the study. A subject is not considered "Lost to Follow-up" until s/he has missed 3 consecutive visits. *A2ALL-Link* will not let a coordinator choose "Lost to Follow-up" as a status unless there are 3 consecutive missed visits. Remember to provide documentation of the missed 3 consecutive visits, and file in the subject's research file/binder.

It is the study coordinator's responsibility to record any change in a subject's status in the database.

Date of death, as well as primary and secondary cause of death, should be entered for subjects who die during the study or are discovered dead when approached for the study.

14.3. Serious Adverse Event (SAE) Reporting

Only report Serious Adverse Events related to the protocol mandated procedures:

- Phlebotomy
- Survey Response
- Height/Weight Measurement
- MRI/CT
- Liver Biopsy

- Pressure and Flow Measurement
- Transient Elastography

If a medical problem occurs during a procedure that is both clinical and research-related, it is not considered a study SAE unless it can be solely tied to the research component of the procedure (i.e., phlebotomy for clinical labs and bio-samples during which patient faints and hits his head).

For an event to be considered as a Serious Adverse Event, one or all of the following must apply:

- Death
- Life threatening
- Persistent or significant disability/incapacity
- Required in-patient hospitalization or prolonged hospitalization
- Congenital anomaly or birth defect
- Important medical events requiring medical or surgical intervention to prevent one of the outcomes listed above

The Serious Adverse Event reporting window for each subject begins with the first study procedure, and ends 30 days after last study procedure.

Serious Adverse Events must be reported to the DCC within 24 hours of the site's awareness of the occurrence. The site should complete the SAE report form in *A2ALL-Link* within this time frame. Once you save the form, notification will immediately be sent to the DCC, DSMB, and NIDDK personnel. Refer to the World Health Organization (WHO) grading scale in the back of the Core Protocol Version 2.1 (Appendix C) for assistance determining events qualifying as Serious Adverse Events.

For additional information about the Core Protocol, please see the list of Frequently Asked Questions included in the MOO as **Appendix X**.

A2ALL: Adult-to-Adult Living Donor Liver Transplant Cohort Study

Core Study Protocol

Version 2.1

March 14, 2013

Original: July 7, 2010

Sponsor
NIH-NIDDK
Project Officers:
Averell Sherker, MD
301-451-6207
Jill Smith, MD
301-451-2025

Protocol Approval

Protocol: A2ALL: Adult-to-Adult Living Donor Liver Transplant Core Protocol	Version / Date: 2.1 / March 14, 2013
IND: N / A	**A2ALL DCC Principal Investigator :** Robert Merion, MD
Study Sponsor: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	
INSTRUCTIONS: The Principal Investigator must print, sign, and date below. The original signature page should be kept in the site's records. After signature, please scan the signature page and email or fax to the A2ALL DCC at the address listed below: Jenya Abramovich A2ALL DCC Jenya.Abramovich@ArborResearch.org Fax: 734-665-2103	
I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 45, 50, 56, and 312, and the International Conference on Harmonization (ICH) document "Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. Further, I will conduct the study in keeping with local, legal, and regulatory requirements. As the Principal Investigator, I agree to conduct and to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission of the A2ALL Steering Committee.	
Site Principal Investigator (Type or Print)	
Site Principal Investigator (Signature)	
Date	

A2ALL Steering Committee
NIH-NIDDK
Project Officers: Averell Sherker, MD
Jill Smith, MD

Data Coordinating Center:
University of Michigan Health System
Principal Investigator: Robert M. Merion, MD (Chair)

Transplant Centers:

Columbia University Medical Center
New York, NY
Principal Investigator: Jean Emond, MD (Co-Chair)

Northwestern University
Chicago, IL
Principal Investigator: Michael Abecassis, MD

University of Pennsylvania
Philadelphia, PA
Principal Investigator: Kim Olthoff, MD

University of Colorado Denver
Aurora, CO
Principal Investigator: James Burton, MD

University of California, San Francisco
San Francisco, CA
Principal Investigator: Christopher Freise, MD

Virginia Commonwealth University – Medical College of Virginia
Richmond, VA
Principal Investigator: Robert Fisher, MD

Lahey Clinic
Burlington, MA
Principal Investigator: Elizabeth Pomfret, MD

University of Pittsburgh Medical Center
Pittsburgh, PA
Principal Investigator: Abhinav Humar, MD

University of Toronto
Toronto, Canada
Principal Investigator: David Grant, MD

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1 Introduction

Adult to adult living donor liver transplantation (LDLT) is a procedure used at major transplantation centers as an alternative to deceased donor liver transplantation (DDLT). The first iteration of the A2ALL study was performed because too few cases were performed at any one center and approaches to the recipient and donor were too diverse across centers to provide reliable and generalizable information on donor and recipient outcomes from individual centers. Therefore, the National Institutes of Health (NIH) organized a network of nine leading liver transplantation centers and a data coordinating center (DCC) to accrue and follow sufficient numbers of patients being considered for, and undergoing, LDLT to provide generalizable results from adequately powered studies. This network established the Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL) that conducted retrospective, prospective and interventional studies of LDLT. In 2009, NIH issued a Request for Applications (RFA) in a competitive process to extend the A2ALL collaborative for another five years (A2ALL-2). Components to be implemented at all sites are a core data and biosample (blood and tissue) collection, intraoperative pressure and flow measurements on all donors and recipients, a liver biopsy at least three years post-transplant for subjects infected with the hepatitis C virus (HCV), and studies of Health-Related Quality of Life (HRQOL) on all donors.

2 Background/Significance

2.1 Overall historical perspective

The procedure of adult-to-adult LDLT is an extraordinary surgical therapy that involves the removal of up to 70% of the volumetric mass of an adult living donor liver and its implantation into an adult recipient. Adult-to-adult LDLT using the right lobe was first performed in Hong Kong in 1996, nearly a decade after LDLT was initiated in pediatric recipients[1,2]. A critical shortage of deceased donor livers, resulting in premature mortality among candidates in need of liver transplantation, remained the single most compelling force driving the need for adult-to-adult LDLT. The waiting list for liver transplantation grew at an alarming rate through the 1990s and early 2000s and has only recently started to stabilize [1]. In the United States, about 16,000 patients are currently on the liver transplant waiting list[1]. Death while awaiting a liver transplant claims more than 2,000 transplant candidates annually[1]. Adult-to-adult LDLT holds the promise of alleviating the donor organ shortage, thereby reducing waiting list deaths and offering improved longevity to patients with end-stage liver disease. Although less than 5% of all liver transplantations in the United States fall into the category of adult-to-adult LDLT, the global trend has been a rapid uptake and widespread adoption outside the United States and Western Europe, notably in Asia[3,4]. Since 1990, more than 7,000 LDLTs have been performed worldwide[5]. The global experience with LDLT is highly skewed towards Asia due to the non-availability of deceased donor programs[3,4,5]. One transplant center in Seoul, South Korea now accounts for nearly 20% of the cases done globally[1]. The total number of adult-to-adult LDLTs performed in the US declined modestly between 2002 and 2008, but the procedure remains widely practiced. Trends suggest improved recipient outcomes, decreases in donor complications, and concerted efforts to standardize donor selection criteria, as well as reporting and management of complications. There have been more than 2,000 cases of adult-to-adult LDLT performed in the United States[6], and the estimated donor mortality rate ranges from 0.24% to 0.4%[7]. Not only is there a trend toward lower rates and diminished severity of donor

complications, but adult-to-adult LDLT is increasingly performed with good results for new categories of patients and under extremely challenging scenarios, such as donation by Jehovah's Witnesses. The practice of adult-to-adult LDLT is likely to expand, as the pressure of the severe deceased donor organ shortage appears to be unremitting. Adult-to-adult LDLT remains the most viable alternative to mitigate the organ shortage, perhaps particularly enticing in patients with hepatocellular carcinoma (HCC) in whom expeditious liver transplantation is desired[6]. As will be described below, however, it is far from clear which candidates are best suited for LDLT. Lastly, adult-to-adult LDLT is being utilized in a small but growing number of patients with acute hepatic failure who must be transplanted within days of developing organ failure.

The objectives of the original A2ALL study were largely accomplished and have resulted in 31 peer-reviewed manuscripts and abstracts that serve as standards for the knowledge of LDLT in the United States. Accordingly, A2ALL has helped define the benefits and risks of LDLT for both donors and recipients. Among these advances are determination of the survival benefit of the recipient who chooses LDLT, recipient and donor morbidity, and resource utilization before and after LDLT. Informed decision-making competence of potential donors has been objectively measured. Disease-specific manuscripts on hepatitis C and HCC outcomes following LDLT as well as reports on the use of LDLT in fulminant liver failure have been published.

Despite A2ALL having achieved many of its original goals, several important questions warrant further research to determine the optimal role of adult-to-adult LDLT in end-stage liver disease treatment. There remain controversies regarding the process of donor consent and the impact of donor hepatic lobectomy on donor medical well-being, psychological health, and QOL. Surgical techniques still need refinement to lower the ongoing high risk of biliary complications in LDLT donors as well as recipients. Although data from the A2ALL study demonstrate a survival benefit of LDLT compared to continued pursuit of a DDLT, better quantification of survival benefit, particularly in selected patient subgroups, has yet to be accomplished. The continuation of A2ALL is critical to address many of these outstanding questions which must be answered to move the field forward. The researchers are in the process of developing research aims and protocols to answer those questions. However, it will take some time to develop these protocols. Since the funding period is limited, it is critical that the core cohort be enrolled and followed for basic key data elements that will form the foundation for the future planned studies.

2.2 Core Protocol data and biosample collection

During its first iteration, A2ALL sites stored about 60,000 serum aliquots and liver tissue samples from approximately 1500 subjects, and 1,121 DNA samples in the NIDDK repositories. The collection of patient and control biosamples and DNA samples from this and other studies for storage in the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) Repositories provides a resource with which researchers can rapidly validate clinical hypotheses and algorithms for clinical decision. The collections also advance the development of diagnostic and prognostic markers, and therapeutics. The repositories allow storage, maintenance, and quality control, and equitable, ethical distribution of biosamples and other resources important to the study of liver transplant. This allows sharing of resources, thus encouraging work by junior investigators, investigators with novel approaches, and others not included in current collaborations, without excluding those who are established in their fields. In addition, collection and storage of DNA samples may increase the sample size and the resulting power of a study to identify genetic

determinants of a disease. It has ensured that research participants are making a maximal contribution, and will decrease duplicative sampling efforts.

The purpose of this core protocol is to serve as a framework for gathering biosamples and accompanying clinical and demographic data from study subjects. These biosamples are a limited and precious commodity, and it is important to collect them as early as possible in the research process.

2.3 Long-term post-transplant outcomes

Adult to adult LDLT began in 1998, and prior to the A2ALL consortium, there had been no adequately powered long-term studies that compared outcomes between recipients of living donor and deceased donor grafts. We plan to continue follow-up on this original cohort of LDLT and DDLT recipients to glean more information on long-term outcomes. Transplant physicians need this information on outcomes to advise prospective recipients about the long-term health consequences associated with choosing to pursue a living donor vs. a deceased donor graft.

2.4 Donor HRQOL study

Optimizing donors' health-related quality of life is a foremost goal for living donor liver transplant programs and an overarching aim of the Adult to Adult Living Donor Liver Transplant Cohort Study 2009-2014 (A2ALL-2). Toward this goal, investigators in the initial A2ALL cohort study (2002-2009) repeatedly surveyed donor status in selected HRQOL domains during the first several years post-donation. These data, while valuable, are limited by poor response rates and the reductions in sample sizes and generalizability resulting from this problem. Moreover, the assessments performed to date do not fully evaluate the occurrence or severity of specific domains of donor psychosocial difficulties that anecdotal reports and single-center studies now suggest are important among living donors[8-18]. There is a critical need to augment the measures used to broadly assess HRQOL in A2ALL to date (e.g., SF-36) with assessments of specific domains that reflect important difficulties that liver donors appear to face not only in the early years but in the long-term after donation. Thus, there appear to be mental health problems, somatic complaints, family interpersonal difficulties, and financial distress that may emerge and even persist after donation. At the same time, any psychological benefits of donation in terms of personal satisfaction and growth also deserve ongoing consideration in order to provide a complete picture of the potential consequences of donation. All of these domains are relevant not only in new prospectively enrolled donors but also for long-term follow-up of previously enrolled donors; long-term living liver donor QOL outcomes have not been described in either A2ALL or other studies.

The proposed A2ALL-2 HRQOL Sub-Study will build upon the A2ALL HRQOL measures employed to date, informed by the A2ALL HRQOL Validation Study, which focuses on identifying the psychometrically strongest measures in the existing assessments to be carried forward into the work proposed herein. Of critical importance, the A2ALL-2 HRQOL Sub-Study will substantially augment these measures with specific assessment of psychiatric symptomatology; somatic symptoms including enduring fatigue and worries about health status; familial relationship strain; financial consequences of donation; and psychological benefits of donation. This carefully selected assessment battery will be deployed in order to study two cohorts of living donors: (a) a long-term donor follow-up cohort, i.e., donors previously enrolled in A2ALL from 2002 forward (all of whom will be > 2 years post-donation when recontacted), enriched by donors who are > 2 years post-

donation recruited from sites that have newly joined A2ALL, and (b) a new prospective cohort, i.e., individuals newly accepted for donation and enrolled in A2ALL-2, and then followed through the first two years post-donation. With each cohort, longitudinal, multi-wave assessments will be conducted in order to examine the prevalence and temporal patterns of change in the HRQOL outcome variables to be assessed, as well as risk factors for adverse HRQOL outcomes.

The strength of the long-term follow-up cohort for addressing these aims will lie in its ability to provide data regarding HRQOL difficulties that emerge and/or persist during the late-term years post-donation. Furthermore, it will be cost-efficient because its first wave of assessments will be partially funded through the A2ALL-2 "Cross-Sectional Long-Term Donor Follow-Up" Study (funded through ARRA). There are no previous studies of large cohorts with extended HRQOL follow-up; such data are at the heart of the mission of A2ALL-2.

The strength of the new prospective cohort will derive from the evaluation of important areas of HRQOL outcomes that have not previously been assessed in large cohorts of liver donors enrolled prospectively. These data will be critical for the future development of protocols designed to sustain HRQOL across the period from before through after recovery from the donation.

2.4.1 The problem

The protection of living donors' well-being and the prevention of any negative consequences of donation are among the highest priorities in transplantation, given that they undergo surgery from which they derive no direct medical benefit. Furthermore, we have an obligation to provide potential donors with information about the long-term implications of liver donation for their well-being. Well-being extends substantially beyond donor medical outcomes and also encompasses HRQOL outcomes. Moreover, there is increasing recognition that it is insufficient to consider these outcomes in only the immediate aftermath of liver donation; these donors require careful, long-term follow-up in order to identify any late-term sequelae associated with donation. Even in the short-term (e.g., first year) post-donation, there is growing concern about negative HRQOL sequelae of living liver donation.[14,15] Unfortunately, these concerns arise largely from anecdotal reports or retrospective analyses of medical records, rather than systematic assessment of a full range of HRQOL outcome domains. A2ALL-2 is well-positioned to provide critical prospective data to address these issues.

2.4.2 Evidence to date

Living liver donors almost uniformly express no regret at having donated, would donate again if that were possible, and report deep feelings of gratification at being able to help another person[8, 15-22] Moreover, generic, non-donation specific, HRQOL assessments of the type employed in A2ALL (e.g., SF-36) show that—at least in the early years post-donation—donors' well-being, on average, meets or exceeds that reported in the general population.[12,19,22-24] Nevertheless, a growing body of qualitative and small cohort studies suggest that significant proportions of liver donors experience major HRQOL difficulties after donation. For example, up to 78% of donors experience high psychological distress and/or meet diagnostic criteria for mood or anxiety disorders[10,11,14], up to 33% report that their health is poorer after donation and that they experience ongoing fatigue and/or pain[15,19,18], up to 50% worry about the lasting effects on their health[9,10,19], up to 20% report worsening and strained relationships with the recipient and/or other family members[25,26], and over 25% have financial hardships with prominent concerns about current and future insurance

status[19,22,27, 28]. Surprisingly, time since donation (at least across the first several years—the focus of virtually all work to date), has not been found to be related to rates of these outcomes. Thus, these problems may persist during the first few years, but whether they persist, worsen or resolve thereafter is unknown. Most worrisome is the fact that the elevated rates of these specific problems are reported in the same literature—and sometimes within the same study—that also reports that generic HRQOL in liver donors meets or exceeds that of the general population. This suggests that generic measures are insensitive when used in living donors and, at best, should be used only as adjuncts to more sensitive, specific assessment of potential problems in donors[8, 29,30].

Particularly alarming is the A2ALL report identifying serious psychiatric problems among donors, including two suicide attempts and one completed suicide[31]. The A2ALL study group noted that their data were very limited given their brief follow-up period (median = six months) and their reliance on medical records reviews rather than prospective assessments[31]. Therefore, it is likely that the rate of psychiatric disorders was greatly underestimated[32,33], suggesting the development of serious psychopathology potentially attributable to the donation experience may be more common, serious, and persistent than previously realized.

The issue of donor financial hardship is also becoming increasingly prominent. In addition to out-of-pocket costs that donors frequently report, significant long-term difficulties in obtaining or retaining health and life insurance can arise[34]. This has led to calls for ongoing monitoring of donors' experiences with insurability and other donation-related financial hardships during not only the initial months but subsequent years following donation[34-36].

In sum, a small literature encompassing anecdotal reports as well as single-site studies of small cohorts clearly points to the need for more focused attention on certain HRQOL outcomes in living liver donors, including psychological status, somatic complaints, familial interpersonal relationships, and financial concerns. At the same time, because donors also report deep satisfaction with having donated (and little to no regret), it is important not to neglect potential psychological benefits when assessing HRQOL in this population. Furthermore, existing work has focused almost exclusively on only the first few months or first year post-donation; long-term HRQOL has received virtually no attention. Finally, existing short-term studies, including work within A2ALL to date, have been limited by poor response rates, high levels of missing data and incomplete follow-up. The work that we propose, encompassing both a long-term donor follow-up cohort and the enrollment of a new prospective donor cohort, is designed to directly address each of these issues. This work will be cost-efficient because it will take advantage of and build directly upon two HRQOL-related studies that will be conducted with ARRA funding. Namely, the "Cross-sectional Long-term Follow-up Study" will provide partial funding and support to collect the first wave of data in the longitudinal long-term follow-up effort that we are now proposing, and the "Validation Study" will provide psychometric evaluation of existing HRQOL instruments employed in A2ALL in order to refine the selection of optimal measures in both study cohorts that we plan to enroll, as described below.

2.5 Intraoperative pressure and flow studies in LDLT recipients

2.5.1 General considerations

Since the beginning of A2ALL-1, there has been enormous worldwide technical progress in improving the operation. As LDLT moved from children to adults, it was observed early that the

size of the graft was related to function in the recipient and that inadequate graft volume led to poor recipient outcomes. Because of the asymmetry of the liver, the right lobe is the larger lobe and right hepatectomy became the procedure of choice in LDLT. Nearly all the transplants enrolled in A2ALL-1 were standard LDLT using the right lobe graft with graft sizes deemed "optimal" for the recipient. Although recipient results were good, removing more than half of the donor's liver remains an operation that is deemed risky for the donor. Consistently using the left lobe as a donor source is appealing as the resection removes only 40% of the donor's liver and thus decreases the chance of liver failure in the donor.

We propose that consistent use of a lesser donor operation will increase acceptability for both the public and the medical community and increase the numbers of LDLT. Because the decreased donor operation will result in a smaller graft for the recipient, it is necessary to develop and validate approaches that permit successful use of smaller donor livers and this is the principal goal of the surgical innovations study anticipated for A2ALL-2. In addition to increasing the use of left lobes, the reliable use of a very small graft will make it possible for smaller donors to donate to larger recipients leading to more LDLT.

The minimum graft size for LDLT has been a subject of study for nearly 15 years. Emond et al. first described the correlation between graft size and function in a series of children and adults receiving LDLT[37]. The pathophysiology of liver dysfunction when the graft is too small has been the subject of numerous publications in both preclinical and human transplant settings. A syndrome of graft injury, cholestasis and the delay of synthetic functional restoration as estimated by the normalization of prothrombin time (INR), has been the general pattern of small liver dysfunction, termed small for size syndrome (SFSS)[38]. Clavien et al. later added the presence of persistent ascites to the definition as the small graft becomes resistant to the passage of blood[39]. Early on, it was suspected that excess portal blood flowing through a limited graft was the cause of graft injury leading to poor function and failure. Animal models and subsequent clinical experience indicates that modulating portal blood flow improves the function and successful transplantation of small grafts. These descriptive studies have only begun to define the parameters that determine what measurements are relevant and what interventions are effective in ensuring the successful use of small grafts in LDLT. Therefore, in A2ALL-2 we seek to prospectively define the limits of graft size, the physiologic parameters associated with alterations of the graft, as well as to validate an algorithm of therapeutic interventions

2.5.2 Effects of pressure and flow on the results of liver transplantation

Surprisingly little is known about normal flow and pressure in the human liver. In partial hepatectomy, it is assumed that the entire portal blood is necessarily directed through the remnant liver. Since the normal liver is soft, it is reasonable to imagine that increased portal blood can flow through the liver up to some limit of compliance[40]. This seems to be an important limit of the amount of liver that can be safely resected. In rodents, 70% resection of the liver is readily tolerated, however an increase of the resection to 85% results in a high mortality[41]. This is better understood in terms of the remnant liver; after 70% resection the remnant is 30% of the liver while only 15% is left behind in 85% resection, a remnant only half as large[42]. Thus, beyond a certain limit of resection, portal flow decreases and pressure increases. The intact host may be able to auto-regulate by constriction of the hepatic artery and the mesenteric artery, decreasing the amount of total visceral blood flow[40,42]. Within the liver, excess portal blood must activate endothelium and local

inflammation, causing damage reflected in enzyme release. Local arterial vasospasm may occur leading to patchy necrosis in the parenchyma[41]. In LDLT and split liver transplantation, a syndrome of poor function associated with grafts smaller than 1% of body weight is characterized by cholestasis and ascites. It is believed that this complication is associated with excess portal flow through the graft and may be prevented/attenuated by interventions to modulate blood flow[43].

2.5.3 Effects of portal flow excess and clinical results of flow modulation in LDLT recipients

Early experience using left lobe grafts lead to markedly reduced recipient survival compared to right lobe grafts with left lobe recipient with 54% survival versus 85% for recipients of right lobe grafts[44,45], with an increased incidence of SFSS since the right lobe is typically 1.5-3 times larger than the left lobe. Patients with normal liver can undergo resection of up to 85% of the liver leaving only 15-20% of the standard liver volume. Recipients of liver transplant often have portal hypertension and can have portal flows 4-7x normal, and decreased arterial flow[46]. Efforts to minimize SFSS have focused on portal flow modulation accomplished by mechanical and/or pharmacologic interventions[39,46,47]. It is likely that severe perfusion injury associated with portal overflow is associated with pathologic endothelial activation in the portal system and the sinusoids. We previously observed severe flow damage in rodents when isolated perfused livers were exposed to excess flow rates (unpublished). In our experiments with machine preservation of human livers, we observed attenuated levels of ICAM-1, IL-8, and TNF-a with optimal preservation[48]. Surprisingly, there is no published data on endothelial phenomena in the small for size liver, though there is undoubtedly severe mechanical stress of the sinusoidal endothelium. A potential protective strategy to optimize flow was reported by Tokunaga et al[49]. Despite the lack of mechanistic work in this area, there is a growing body of empiric clinical and pre-clinical evidence that portal flow attenuation, at least transiently, is protective of the small liver remnant. *We propose that early portal flow attenuation is protective, though, over time, the hepatotrophic benefits of portal blood to the liver need to be restored.* In the clinical arena, there is conflicting data between the harm of portal flow and the consistent correlation showing an association between high portal flow and eventual regeneration[50]. Portal modulation may be accomplished by vasopressin for splanchnic vasoconstriction, somatostatin, splenic artery ligation, splenic artery embolization, splenectomy and portocaval shunts[46, 51, 52]. Splenic artery ligation in a small series has been shown to decrease portal flow by 33% in patients undergoing liver transplantation. Yamada et al found that hemi-portocaval shunting reduced portal flow by 33 and 50%[46]. Using this approach, they were able to transplant a series of extra-small grafts. Liver compliance has been equated to portal venous flow divided by portal venous pressure[41]. Thus optimal graft performance would be found with a high compliance graft with high portal flow and low portal pressure with a relationship of better performance of the liver tissue at higher flow until limits are exceeded and pressure begins to rise significantly. We seek to demonstrate that by altering portal flow, we can modulate compliance in the allograft and thus enable the use of smaller grafts.

2.6 Late evidence of fibrosis progression after LDLT or DDLT for HCV

HCV recurrence after liver transplantation is universal in patients who are viremic pre-operatively. Chronic hepatitis evolves to cirrhosis at a variable rate, but more rapidly than in non-transplant patients; ~20% of patients develop cirrhosis within 5 years of LT. Initial studies suggested that outcomes for recipients of LDLT with HCV were inferior to recipients of DDLT with HCV, with higher rates of graft loss, more frequent occurrence of severe cholestatic hepatitis, and higher rates

of cirrhosis[53-55]. However, subsequent studies, including results from the A2ALL-1 Study cohort, showed similar graft and patient survival once centers had mastered the technical aspects of the LDLT procedure[45,56-59]. In the A2ALL-1 cohort of 181 LDLT and 94 DDLT HCV-infected recipients, overall 3-year unadjusted graft survival was 68% for LDLT versus 80% for DDLT (p = 0.04), respectively. However, when analysis was restricted to LDLTs after the first 20 cases at each center, graft survival in recipients of LDLT and DDLT were not significantly different, 79% versus 80%, respectively (p=0.74)[56]. A significant limitation of the first A2ALL study is the fact that protocol liver biopsies were missing in approximately one third of recipients, and follow-up liver biopsies obtained more than 3 years post-transplant comprised only a small fraction of the liver biopsies available for analysis.

Initial studies of HCV disease progression reported higher rates of severe HCV recurrence in LDLT compared to DDLT recipients, observations which have not been confirmed in subsequent studies. However, studies to date are limited in the duration of follow-up, with most reporting disease progression up to only 2-3 years post-LT, and in relatively small patient populations. Thus, the outcome of HCV recurrence after LDLT vs. DDLT requires further study for longer periods of follow-up and in larger patient populations; patients enrolled in Retro and Cohort A2ALL-1 are ideally suited to answer this critical question.

Clinical factors influencing the rate of HCV disease progression and risk of graft loss have been well-described in DDLT, but not LDLT, recipients[60]. The factors most consistently linked with higher risk of recurrent cirrhosis in DDLT recipients include older donor age[61,62], prolonged cold ischemia time, cytomegalovirus infection, acute cellular rejection requiring treatment, and post-transplant insulin-resistance or diabetes. The importance of donor factors is also very apparent, especially older donor age[61]. Using donors under the age of 40 years as a reference group, an increasing risk of graft loss is seen with HCV-infected transplant recipients with donors between the ages of 41-50 years [HR = 1.67; 95% CI (1.34-2.09)], donors between 51-60 years [HR = 1.86; 95% CI (1.48-2.34)] and donors > 60 years [HR = 2.21; 95% CI (1.73-2.81)][62]. Most LDLT recipients with HCV have younger donors, which would be predicted to improve outcomes; however, this possibility has only been evaluated in a single center with a relatively small study population[59]. An important aspect of this study proposal will therefore be to evaluate whether risk factors for aggressive HCV recurrence after DDLT also apply to LDLT recipients in long-term follow-up.

2.7 Pain Control in Living Donors Following Partial Hepatectomy: Measuring the Quality of Care

Physicians use anecdotal evidence or empiric reasoning to select postoperative pain care for live liver donors due to a lack of evidence guiding clinical decision-making. Consequently, the transplant community has no objective information about pain management in live liver donors to use for quality improvement. Recently, the American Pain Society (APS) developed a validated tool to measure the quality of pain management. The tool assesses multidimensional aspects of pain care. We propose a two part study: to survey centers to understand the previous experience with pain management and to use the APS tool to measure quality outcomes with pain care.

There is insufficient data to determine if one approach to pain treatment is better or safer than another in live liver donors. The choice of pain care is therefore empiric or based upon anecdotal evidence. Only two single center studies have reported pain management outcomes in live liver

donors[76,77]. Each used a different care plan and method to measure outcome. Consequently, little is known about the current approach to pain management in live liver donors. Further, the existing findings cannot be compared with other centers because there is no standardized means to measure outcome. Thus, there is no method to conduct quality improvement for postoperative live donor pain management.

The American Pain Society recently issued a Patient Outcome Questionnaire-revised (APS-POQ-R) that was validated to measure patient satisfaction[77]. The APS-POQ-R identified specific features of pain management that predict patient satisfaction[77]. These include: ongoing assessment, interdisciplinary collaborative care that includes patient input and treatment that is efficacious, cost conscious and culturally appropriate. These features are incorporated into the questions used to measure quality indicators. These characteristics are consistent with the concept of quality that encompasses the structure, process and outcome of pain management.

The revised tool for pain assessment is inclusive. It measures outcome as patient satisfaction. A low pain score (little reported pain) did not guarantee that patients were satisfied with their care[77]. Rather, patient satisfaction (outcome) was highly influenced by interactions with the care providers; the resources available at each site and the nature of the interactions.

The APS-POQ-R collects data about side effects, but does not collect information about more serious complications that could be related to pain management. For example, pneumonia may occur more frequently in patients who experience poor pain relief or have a high degree of sedation[78]. Additional information is needed to fully examine the relationship between pain management and outcome.

Postoperative pain management in live donors can be significantly improved if efficacy is measured in a consistent way. This can be done by using a single set of validated tools to measure the safety and quality of pain control in a multi-institutional study cohort. This should generate findings that can be generalized to other clinical settings. The data can be used to set quality-based goals for pain management in all live liver donors. The APS-POQ-R meets the stringent criteria needed to evaluate outcome and the A2ALL Consortium already has a uniform assessment tool to measure complications.

3 Specific Aims/Study Objectives/Hypotheses

The following table shows the categories of patients that are relevant for each of the Aims (1 through 6) below (R=recipients; D=donors).

		Era of Transplant or Donation		
		A2ALL-1 Cohort (or analog at new centers)	Gap	A2ALL-2
Continuing A2ALL -1 Centers	LDLT	**R: 1,2,5; D: 1,3**	**R: 1,2; D: 1**	**R: 1,2,4; D: 1,3,4,6**
	DDLT	**R: 1,2,5;**		
New A2ALL Centers	LDLT	**R: 1,2,5; D: 1,3**	**R: 1; D: 1**	**R: 1,4; D: 1,3,4,6**
	DDLT	**R: 5;**		

3.1 Primary Aim 1: To collect data and biosamples prior to, during, and after LDLT among all donors and recipients for use by other A2ALL protocols and future studies.

3.1.1 Objectives

- To facilitate and inform studies of samples and data collected, thus enhancing the value of this and future investigations.
- To continue contributing to the NIDDK genetics, biosample and data repositories so that current and future questions regarding liver disease, living donation and liver transplantation can be investigated by A2ALL and external researchers as new technologies and resources become available.
- To ensure that samples are stored under uniform conditions, and to simplify access by other scientists to samples. Similarly, study datasets will be maintained to facilitate new analyses after the study closes.

3.2 Primary Aim 2: To characterize the differences between LDLT and DDLT in terms of recipient post-transplant outcomes including patient and graft survival, surgical morbidity, and resource utilization.

3.2.1 Objectives

- To continue to discern the long-term risks and benefits associated with choosing a living donor vs. deceased donor liver transplant with respect to the following metrics:
  - Patient and graft survival analysis starting from the time of transplantation
  - Comparison of the incidence of defined medical and surgical complications after transplant between LDLT and DDLT
  - Comparison of resource utilization (hospitalization) between LDLT and DDLT.

3.3 Primary Aim 3: To determine the prevalence, course, and predictors of poor HRQOL outcomes associated with living liver donation.

Measures used to broadly assess HRQOL in A2ALL to date (e.g., SF-36) will be augmented with assessments of specific domains that reflect important difficulties that liver donors appear to face not only in the early years, but long after donation.

A cohort will be assembled consisting of (a) all A2ALL donors previously enrolled in A2ALL from 2002 onward, all of whom will be >2 years post-donation at re-enrollment, enriched by the addition of (b) all living liver donors >2 years post-donation recruited from the new A2ALL-2 sites (Pittsburgh, Toronto, Lahey). This enriched cohort will receive a “baseline” assessment at time of (re)contact, and they will be surveyed annually for the next 3 years in order to achieve the following objectives:

3.3.1 Objectives – Long-term donor follow-up cohort

- To determine the prevalence and course of change in poor HRQOL outcomes in five domains during the extended years after donation:

- Clinically significant psychiatric symptomatology related to depression and anxiety
- Enduring fatigue, other somatic symptoms, and lasting health concerns
- Negative changes in relationships with the transplant recipient and/or other family members
- Financial strains related to health-related expenses and to changes in employment, and health-, Disability- or life-insurance benefits.
- Reductions in global/overall HRQOL

- To determine the prevalence and course of change across time in positive psychological outcomes of donation, including satisfaction with donation and personal growth related to the experience.
- Among donors followed since donation, to examine whether pre-donation characteristics (e.g., demographics, motivations and ambivalence about donating) and medical factors (e.g., perioperative complications) predict poor HRQOL at baseline and predict persistently impaired HRQOL across the study period.

3.3.1.1 Hypotheses:

In the long-term years post-donation:

- the prevalence of poor HRQOL outcomes at initial follow-up contact will be higher than the rates of these problems in normative (population-based) samples,
- based on studies in kidney donors, we hypothesize that ~30% of liver donors will experience clinically significant (above-threshold) HRQOL impairment at initial follow-up contact.
- Concerning course and predictors of HRQOL:
  - on average across the follow-up assessments, we expect that donors who have clinically significant HRQOL impairment at baseline will be likely to continue to show such impairments over time
  - we also expect the differences between “screen positive” and “screen negative” donors will grow smaller with time, i.e., the rates of some problems, e.g., financial strains, will not only persist in the “screen positive” donors but will show a steady increase in the long-term years in the “screen negative” donors
- risk factors such as higher ambivalence about donating and perioperative complications will increase the likelihood of showing poor HRQOL at study entry and of showing persistently impaired HRQOL across the study period.

3.3.2 Objectives – Prospective donor cohort

A cohort will be assembled consisting of all individuals approved as liver donors at A2ALL-2 sites. These subjects will be enrolled and assessed pre-donation, and at 3-, 6-, 12-, and 24-months post-donation. The following objectives will be addressed:

- To examine the post-donation prevalence, and trajectory of change from pre-donation through two years post-donation, of poor HRQOL outcomes in five domains:
  - Clinically significant psychiatric symptomology related to depression and anxiety
  - Enduring fatigue, other somatic symptoms, and lasting health concerns
  - Negative changes in relationships with the transplant recipient and/or other family members

  - Financial strains related to health-related expenses and to changes in employment and health-, Disability- or life-insurance benefits
  - Reductions in global/overall HRQOL.
- To determine the prevalence rates and trajectory of change in post-donation positive psychological outcomes reflecting personal satisfaction and growth related to the experience.
- To examine whether pre-donation characteristics (e.g., demographics, motivations and ambivalence about donating) and medical factors (e.g., perioperative complications) predict which donors are at risk for poor outcomes in the domains listed above.

3.3.2.1 Hypotheses:

- The prevalence of poor HRQOL will increase from pre- to post-donation,
- the prevalence of poor HRQOL outcomes post-donation will be sustained through the first year post-donation, show some improvement during the second year, but not return to pre-donation levels,
- the majority of donors will report satisfaction and growth related to the donation experience,
- risk factors such as higher ambivalence about donating and perioperative complications will increase the likelihood of poor HRQOL outcomes and decrease their likelihood of sustained satisfaction and personal growth.

3.4 Primary Aim 4: To study the effects of pressure and flow on the outcomes of LDLT.

3.4.1 Objectives

The main objectives of this aim are to:

- Establish the normal hepatic blood flow and portal compliance in the human liver
- Determine the relationship between hepatic flow and pressure, and graft size and function and clinical outcomes in living donor liver transplantation
- Establish the benefit, if any, of portal flow modulation interventions on hepatic compliance, and functional and clinical outcomes.

3.4.1.1 Hypotheses:

- It is generally thought that the limits of portal compliance are exceeded when graft size is less than 40% of normal (<.8% of liver/recipient body weight ratio (BWR). We hypothesize that grafts smaller than this limit will demonstrate altered hemodynamics, limited compliance, and impaired function.
- We hypothesize that restoration of pressure and flow in the “normal” range will permit grafts below 0.8% BWR to function normally with good results.

3.5 Primary Aim 5: To compare the long-term histological outcomes in recipients of LDLT and DDLT with recurrent HCV infection.

3.5.1 Objectives

To determine whether recurrent hepatitis C in LDLT recipients is associated with less severe histological fibrosis (particularly, slower rate of progression to cirrhosis) compared to DDLT recipients.

3.5.1.1 Hypothesis:

Living donor liver transplant (LDLT) recipients will demonstrate slower rate of progression to cirrhosis than deceased donor liver transplant (DDLT) recipients as determined by histology. Given that little difference has been seen in the initial 3 years post-transplant, we anticipate that any difference will be expressed more than three years post-transplant.

3.6 Primary Aim 6: To understand the history of pain management and to measure quality of care in pain control in living donors following partial hepatectomy.

3.6.1 Objectives

- To understand each institution's previous experience with pain management in living donors utilizing a retrospective survey (see Appendix E) of appropriate medical staff to:
  - Determine all methods and personnel at each center used to manage postoperative pain in live liver donors since the start of their program
  - Identify how pain was assessed during the postoperative period (current and previous assessment methods)
  - Identify methods care providers used to assess the outcome (quality) of pain management.
- To measure the quality of postoperative pain management in live liver donor and identify areas for improvement. After implementing a single method (patient survey instrument) for reporting quality indicators at all nine A2ALL centers (see Appendix F), the investigators will:
  - Assess overall patient satisfaction with pain management
  - Assess satisfaction with aspects of pain management thought to affect overall patient satisfaction
  - Identify quality indicators that differ in overall donor satisfaction

3.6.2 Hypothesis

Using these methods, we reason that individual centers may perform equally well using different approaches to pain management and suggest that variations in the quality of a patient's experience will be influenced by the structure and process of care.

4 Investigational Plan

4.1 Primary Aim 1: To collect data and biosamples prior to, during, and after LDLT among all donors and recipients for use by other A2ALL protocols and future studies.

4.1.1 Study methods

In order to maximize the study population, there are several cohorts of subjects who will enter the protocol, based on:

- Their previous enrollment in the original A2ALL Cohort Study.

- Whether their clinical care occurred/is occurring at one of the new consortium centers. When the project was renewed, three of the original A2ALL clinical centers' funding was not renewed, and three new centers were added to the consortium (University of Toronto, Lahey Clinic and University of Pittsburgh Medical Center).
- When the transplant/donation occurred. In order to have a contiguous sample, those subjects from the original sites and new sites whose transplant/donation occurred during the period of time that began with the end of enrollment into the original Cohort study (Aug. 31, 2009) and ends with opening of enrollment in the current core protocol (February, 2011); this is referred to as the "Gap Era".

Subjects who enroll after their donation/transplant will join the protocol schedule of events at the next scheduled visit time point in the study, with interim data collected by chart review. Those who have already reached study endpoints (death or graft failure) will have follow-up data collected through the endpoint under waiver of consent.

Enrollment for LDLT recipients and donors who were not in the A2ALL-1 Cohort Study or from the gap era will occur prior to living donation.

Biosamples will be collected from donor and recipient subjects preoperatively, intraoperatively, and at selected times postoperatively (see Appendices A and B).

Clinical and demographic data will be collected from the subjects preoperatively, intraoperatively, and at selected times postoperatively (see Section 4.1.3) in order to carry out planned studies researching topics in immunosuppression minimization, regeneration, HCC, HCV treatment and recurrence, and analysis of intraoperative and perioperative factors that affect graft and patient survival. The DCC plans to periodically update outcomes and mortality information (graft failure, liver failure, mortality) in the study population by linking to the Scientific Registry of Transplant Recipients (SRTR).

The NIDDK Central Repositories are two separate contract-funded components that work together to store data and samples from significant NIDDK-funded studies. One component is the Biosample Repository, which will gather, store and distribute biological and genetic samples from studies. The second component is a Database Repository that will gather, store and distribute the incremental or finished datasets from studies.

The collection of subject biosamples and DNA samples from this and other studies for storage in the Biosample and Data Repositories has the potential to become a resource with which researchers can rapidly validate clinical hypotheses and algorithms for clinical decision-making. The collections will also advance the development of diagnostic and prognostic markers, and therapeutics. To date, no such collection has been available to the investigators interested in studying liver disease and transplant issues. The repositories will allow storage, maintenance, and quality control, and equitable, ethical distribution of biosamples and other resources important to the study of liver transplant. This will allow sharing of resources, thus encouraging work by junior investigators, investigators with novel approaches, and others not included in current collaborations, without excluding those who are established in their fields. In addition, the genetics samples may increase the sample size and the resulting power of a study to identify genetic determinants of a disease. It will ensure that research participants will be making a maximal contribution, and will decrease duplicative sampling efforts. During its first iteration, A2ALL sites stored more than 60,000 serum

aliquots and liver tissue samples from approximately 1500 subjects in addition to 1,121 genetics samples in the NIDDK repositories. A2ALL is committed to sharing the resources collected in this study with current and future researchers via the use of the NIDDK repositories.

4.1.2 Participant selection

All potential subjects will be presented with information and approached for consent to have their biosamples, genetic material and deidentified data stored in the NIDDK repositories for future study.

4.1.2.1 Inclusion criteria

- Recipients
  - Age 18 or older at the time of consent
  - Has had a living donor identified and accepted and LDLT is planned
  - Informed consent obtained
  - Is listed for single organ (liver) transplantation

- Donors
  - Age 18 or older at the time of consent
  - Has undergone donor evaluation process and was accepted and donation surgery is planned
  - Informed consent obtained

4.1.2.2 Exclusion criteria

  - Prospective donors and recipients should not have undergone transplant/donation surgery prior to consent.

4.1.3 Data elements

- **Recipients**
  - Liver function tests (LFTs) – baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), Month 1, Month 3, Month 12 and annually thereafter
  - Complete blood count (CBC) – baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), Month 1, Month 3, Month 12 and annually thereafter
  - BUN baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), and at Month 1
  - Serum Creatinine - baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), Month 1, Month 3, Month 12 and annually thereafter
  - Sodium - baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), and at Month 1
  - Coagulation (PT/INR) – baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), Month 1, Month 3, Month 12 and annually thereafter
  - Imaging studies of the liver and spleen at Baseline and 3 months post-transplant
    Demographics

- Cause of liver disease
- Intraoperative data (warm and cold ischemia time, estimated blood loss, length of operation, etc.).
- Medical history
- Post-operative morbidity
- Clinical information (indication and pathology report) for all "for cause" liver biopsies (rejection episode confirmation, elevated LFTs, suspected HCV recurrence, etc.).
- For subjects with hepatocellular carcinoma (HCC), clinical information regarding tumor characteristics will be collected.
- Hospitalizations, survival status and cause of death in those who died
- Whole blood – collected for genetic analysis/DNA studies for extraction by the study's contracted DNA Core Lab (Fisher BioServices), and storage in the NIDDK Biorepository (one-time collection)
- Serum – collected pre-operatively, and postoperatively at Week 1, Week 2, Month 1, Month 3, Month 12, and annually thereafter, for storage in the NIDDK repository
- Plasma and peripheral blood cells – collected pre-operatively, and post-operatively at Month 1, Month 3, Month 12, and Month 24 postoperatively, for storage in the NIDDK repository
- Whole blood for extraction of RNA – collected pre-operatively, and post-operatively at Month 1, Month 3, Month 12, and Month 24 postoperatively, for storage in the NIDDK repository
- Liver tissue collected intraoperatively while graft is on the back table, and 1 hour after arterial and portal venous reperfusion prior to closure for storage in the NIDDK repository and for genomic analysis of regeneration

- **Donors**
  - LFTs - baseline, postoperatively at Week 1, Month 1, Month 3, Month 12 and annually thereafter
  - CBC - baseline, postoperatively at Week 1, Month 1, Month 3, Month 12 and annually thereafter
  - BUN and serum creatinine - baseline, postoperatively at Week 1and Month 1
  - Coagulation (PT/INR) - baseline, postoperatively at Week 1, Month 1, Month 3, Month 12 and annually thereafter
  - Demographics
  - Relationship to recipient
  - Intraoperative data (lobe donated, estimated blood loss, donated lobe weight, length of operation, etc.).
  - Liver tissue collected intraoperatively just prior to resection, closest to the line of resection and at one hour post-resection, or prior to closure, for storage in the NIDDK repository and for genomic analysis of regeneration
  - Medical history
  - Post-operative morbidity
  - Imaging studies of the liver and spleen pre-operatively and at 3 months post-donation
  - Hospitalizations

- Whole blood – collected for genetic analysis/DNA studies for extraction by the study's contracted DNA Core Lab (Fisher Bioservices), and storage in the NIDDK Biorepository (one-time collection)
- Serum – collected preoperatively and postoperatively at Week 1, Month 1, Month 3, Month 12 for storage in the NIDDK repository
- Plasma and peripheral blood cells – collected preoperatively, and at Month 1, Month 3, and Month 12 postoperatively, for storage in the NIDDK repository
- Whole blood for extraction of RNA – collected preoperatively and postoperatively Month 1, Month 3, and Month 12 for storage in the NIDDK repository.

4.2 Primary Aim 2: To characterize the differences between LDLT and DDLT in terms of recipient post-transplant outcomes including patient and graft survival, surgical morbidity, and resource utilization.

4.2.1 Study methods

In the A2ALL-1 Cohort Study, recipient candidates who were eligible to receive a living donor graft, but received a deceased donor graft (DDLT) were followed in the study. In order to characterize differences between DDLT and LDLT post-transplant outcomes, DDLT recipients who participated in the A2ALL Cohort Study will be approached for consent into the A2ALL-2 Core Protocol for continued data and specimen collection.

A2ALL-1 Cohort Study LDLT and DDLT recipients will join the protocol at whatever post-transplant time point they have reached, with interim follow-up data collected by chart review. Those who have already reached study endpoints (death or graft failure) will have follow-up data collected through the endpoint by waiver of consent.

All A2ALL centers will consent and enroll willing eligible LDLT recipients from the "Gap Period" who have not yet met study endpoints, with retrospective data obtained by electronic medical records or chart review; for those who have met study endpoints, data will be collected under waiver of consent. Prospective post-transplant data and biosamples will be collected from this population as is described in Primary Aim 1 for LDLT recipients.

4.2.2 Participant Selection

All potential subjects will be presented with information and approached for consent to have their biosamples, genetic material and deidentified data stored in the NIDDK repositories for future study. Please see Appendix D to view a table detailing subject eligibility by site type, graft type and study era.

4.2.2.1 Inclusion Criteria

- Age 18 or older at the time of consent
- Had a living donor identified and receipt of an LDLT was or is planned, and
- Received an LDLT graft, or donated in the Gap Period (all sites)
- Received a DDLT graft (continuing sites only)
- Participated in the A2ALL-1 Cohort Study (continuing sites only)
- Informed consent obtained

4.2.2.2 Exclusion criteria

- Prospective subjects should not have undergone transplant/donation surgery prior to consent.

4.2.3 Data elements

See Section 4.1.3.

4.3 Primary Aim 3: To determine the prevalence, course, and predictors of poor HRQOL outcomes associated with living liver donation.

4.3.1 Study methods – Long-term donor follow-up cohort

Sample: The sample will consist of all donors undergoing surgery in 2002 or later who were enrolled during the first A2ALL study period, and who are >2 years post-donation at time of recontact. This sample will be enriched through enrollment of donors >2 years post-donation who underwent surgery during the same time period, from new A2ALL sites. American Recovery and Re-investment Act (ARRA) funding from the A2ALL-1 "Cross-sectional Long-term Follow-up Study" will be utilized to re-consent and re-enroll existing A2ALL donors and conduct the first follow-up reassessment with them; thus the additional costs of enrollment will be limited to recruiting and consenting donors from new A2ALL sites.

All donors will receive a baseline assessment and will be reassessed annually for the next 3 years using the same assessment battery.
We expect a sample size of 600 at the baseline assessment (see Section 4.3.4, Sample size and power calculations, below).

Procedures: The procedures to be utilized have been deployed successfully in other multi-site longitudinal survey research with living donor and other patient populations. They are designed to maximize recruitment and retention and thereby avoid many of the difficulties experienced in the HRQOL studies during the initial A2ALL funding period (see also Section 6, Study Management). All donors consented during the first A2ALL study period will require re-consenting, and donors recruited from new A2ALL sites will need to provide informed consent (see Human Subjects section below). They will be approached for re-consent (or for first-time consent at new sites) either during the first year of A2ALL-2 funding (near the anniversary date of their donation) or as soon as they are > 2 years post-donation. The requirement that they be > 2 years post-donation for enrollment in the long-term cohort was selected for three reasons. First, the vast majority of existing HRQOL studies of living donors focus on the first 1-2 years post-donation; there is a dearth of evidence on longer-term HRQOL outcomes. Second, even the most recently enrolled donors in the original A2ALL cohort will advance beyond 2 years post-donation during the period of A2ALL-2 and thus be eligible for enrollment. Third, these new data from > 2 years post-donation, considered in concert with the evaluation of identical outcome areas up to 2 years post-donation in the new prospective cohort study described in Section 4.3.2, below, will provide seamless coverage of understudied outcomes (e.g., psychiatric symptomatology) from pre-donation through many years post-donation.

The decision to use 2002 as the earliest year in which donors could have donated and be eligible for the long-term follow-up stems from several considerations. First, there is a diminishing return for the investment of attempting to relocate and contact individuals as time since donation increases.

Second, the pool of available donors becomes markedly smaller in years earlier than 2002 at the A2ALL sites. Third, we reasoned that individuals who donated earlier than 2002 did so during a period in which many centers were developing their expertise in living donor surgery and thus there could be marked "era" effects if we included individuals enrolled during the very early years of centers' practice of living liver donor surgery.

Once the long-term donors are enrolled, they will be re-assessed annually for 3 years. The rationale for repeated assessments of donors rests on the need to chart the course of changes in these donors' HRQOL outcomes during a time period for which virtually no empirical information is currently available.

The study will utilize telephone-based survey methods to collect data at each assessment time point. A centralized approach to data collection will be utilized in order to maximize response rates and retention in the study (see Section 6, Study Management, below). Thus, donors will be informed during the re-consenting process (or initial consenting for donors from new A2ALL sites) that their contact information will be forwarded to the survey research center responsible for data collection, and survey center personnel will then contact each donor to complete the telephone surveys. The re-consenting (or initial consenting at new sites) will be performed by a member of the A2ALL team located at each site. After the completion of each of a total of 4 surveys (the initial follow-up, and 3 annual surveys thereafter), each donor will be paid $20 for each completed survey. It is essential to provide such payments in order to maximize recruitment and retention and demonstrate appreciation for donors' efforts. Used alone, the promise of payment incentives consistently boosts response rates by 20%-30%.[69,70]

4.3.2 Participant selection

4.3.2.1 Inclusion criteria:

- All donors previously enrolled in A2ALL will be eligible if they are now >2 years post-donation and donated in 2002 or later.
- All donors from new A2ALL sites who meet these criteria will also be eligible. They will be enrolled utilizing the procedures specified above.

4.3.2.2 Exclusion criteria

- Inability to comprehend spoken English

After informed consent is obtained by staff at individual centers, all assessments will be conducted by telephone; no visits will be required. As noted above, donors will complete a maximum of four assessments.

4.3.3 Data elements

Table 1 lists the measures to be included in the first of the three annual telephone assessments. (Subsequent assessments are identical to the first assessment except that one item about recovery and two demographic items are omitted, and the time frame for some of the items is modified to cover the period since prior assessment.) Our selection of measures was guided by the following principles: for domains not previously assessed in A2ALL (e.g., mental health, somatic issues such

as fatigue), new measures were selected that met two criteria: (a) they have known psychometric properties and have been used extensively in donor and/or other relevant populations and (b) they are brief. For domains previously assessed in A2ALL (e.g., positive psychological outcomes of donation), we will retain and/or augment existing measures rather than replace them with new measures. We have proposed the measures most likely to be retained; results of the A2ALL "Validation Study" (funded through ARRA) will provide additional guidance on which of the candidate measures to be retained also show the strongest psychometric properties.

778 **4.3.3.1 Table 1: HRQOL measures for long-term donor follow-up cohort, Time 1**

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Domain	Specific Items in Survey	Total No. of Items
Demographic items	34, 42, 43, 57 – 60	7
Mental health • PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)[63]	39a-i, 40a-g, 41, 41a-e	11 to 22**
Somatic complaints • FACIT-Fatigue[64] • Brief Pain Inventory Short Form: numeric rating + activity impairment subscale[65] • Post-Donation Symptom Checklist[20,25] • Post-Donation concerns about health (Simmons Worries about Donation items, Simmons Donation Stressfulness items; general QOL physical items)	 29a-m 28, 28a-g 27a-s 1, 9-15, 51, 52, 54, 61	 13 1 to 8** 19 12
Interpersonal relationships • Relationship with Recipient items (Simmons and general QOL items) • Simmons Family Support items • Simmons Worry about Recipient item • Toronto Recipient Behavior item • Simmons Preoccupation items • Simmons Grief items	 30, 32, 32e-j 33, 35 32d 32k 7, 31 32a-c	 2-14** 1-2** 1** 1** 2 4**
Financial concerns • Financial Burden of Donation items[28,66]	 44-48, 49a-d, 50	 10
Positive psychological outcomes • Simmons Better Person scale items • Simmons Satisfaction with donating items • Campbell Global Life Satisfaction item • Regret item from general QOL items • Posttraumatic Growth Inventory[67]	 2-6, 36a-c, 55, 56 8a-g 38 53 37a-j	 10 7 1 1 10
Generic HRQOL • SF-36v2	 16, 17, 18a-j, 19a-d, 20a-c, 21-23, 24a-i, 25, 26a-d	 36
Total No. of items/duration of assessment		146 to 176/** 25 to 40 min***

*most of the measures and items are copyrighted and are reproduced with permission
**depending on whether respondent skips out of sections
***estimate based on pilot testing

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We anticipate a total sample size of 300 donors from the existing A2ALL cohort, enriched with 300 additional donors from the new A2ALL sites (Total N = 600). This sample size estimate is based on the sampling frame requirements described above, an assumption that we will be unable to locate 10% of donors despite using state-of-the-art internet-based search strategies for donors lost to follow up at centers, and an assumption that 20% to 30% of donors recontacted will refuse to provide consent for a long-term follow-up study. Furthermore, across 3 years of follow-up, we anticipate (based on our past experience in following transplant-related samples using the type of survey strategies described earlier), that attrition will range between 10% to 15%.

With a sample of 600 donors at the initial assessment, our power to detect whether the rate of poor HRQOL in the donors differs from a population/normative rate (at alpha < .05, two-tailed) exceeds .995, even for very small differences of less than 2% between the observed and normative rates (Specific Aim 2, Objectives a.1. and a.2.). For hypotheses focused on specific effects or relationships, our power exceeds .80 at alpha = .05, two tailed, for moderate-sized[68] effects even if as much as 50% of the sample is lost to attrition (a percentage much higher than expected, as noted above). We note that we will not restrict our analyses to consideration of outcomes at only individual time points but will utilize a mixed effects approach (which is appropriate both for interval and discrete outcomes). Power will be even greater under a mixed effect approach because such models allow for the inclusion of cases with incomplete data, and thus our effective sample size will be the total cohort enrolled. Therefore, even if we apply corrections for multiple comparisons (given the fact that we will examine multiple domains of HRQOL), our power will continue to exceed .80 for examining relationships such as risk factor-outcome associations.

4.3.4 Sample size and power calculations

Not applicable for this cohort.

4.3.5 Statistical analysis

A critical component of the analyses is to provide descriptive information about the long-term follow-up cohort at each follow-up time point post donation (Specific Aims a.1. and a.2.). Standard approaches to examine distributions of responses to survey measures will be examined (e.g., descriptive statistics, box plots, histograms). An important goal is the examination of prevalence of poor HRQOL outcomes in each identified domain at the initial assessment. We will examine the percentage of the cohort at study entry that report clinically significant difficulties within a given domain (e.g., in the mental health domain, the percentage who meet diagnostic criteria for major depression, generalized anxiety disorder, or alcohol abuse). These rates, as well as mean scores on continuous measures, can be compared to norms for the measures in order to determine whether the cohort is experiencing more or fewer difficulties than community-based or other patient samples.

Other key analytic goals focus on course and predictors of poor HRQOL. We have two hypotheses about course, as well as hypotheses about predictors (see Specific Aims, list of hypotheses). Mixed effects models will be used to examine the hypotheses. These models will allow us to examine temporal patterns of responses in each outcome domain. We will evaluate assumptions regarding missing data patterns and mechanisms and engage in sensitivity analyses to test the stability of our models. To examine risk factors for poor outcomes in the identified domains at (or by) a particular time point post-donation, we will initially utilize regression-based strategies (linear, logistic, or Cox proportional hazard, depending on the outcome measure of interest).

We will engage in additional exploratory analyses in order to determine whether, in the donors followed longitudinally, we can identify distinct temporal patterns of change (or lack thereof) over time. There are several latent structure techniques that can be used for this purpose (e.g., cluster analysis as well as trajectory modeling and growth curve analysis). These techniques can be used to identify subgroups of individuals according to how persistently they show HRQOL impairment in a given area. Thus, we might expect to observe (a) a group who show persistent impairments (impairments observed at a majority of assessment time points), (b) a group for whom the proportion with impairment increases, (c) a group with consistently low rates of impairment and (d) a group whose rate of impairment fluctuates over time with no consistent pattern. If we identified such groups, we could then examine whether they differ as a function of other variables (e.g., pre or early post-donation characteristics). The ability to predict group membership is important because clinical education and early intervention efforts to potentially avoid or limit HRQOL impairments could be more precisely targeted.

4.3.6 Study methods – Prospective donor cohort

Sample: All English-speaking individuals approved for living donation at A2ALL sites during the enrollment period of A2ALL-2 will be recruited.

Study design: prospective single-arm repeated measures (assessments pre-donation, and 3 months, 6 months, 1 year, and 2 years post-donation).

Procedures: The procedures to be utilized resemble those described above for the long-term follow-up cohort and are designed to maximize recruitment and retention across the 2-year observation period. The decision to follow the sample for 2 years was made for two reasons. First, the first several years post-donation are described as an important period of adaptation following living donation, yet little is known about the HRQOL difficulties that may emerge in liver donors during this period in the domains to be examined. Second, the follow-up in the long-term cohort will begin at >2 years and we noted above that, across the two cohorts described in the present protocol (i.e., the long-term and new prospective samples), we will collect previously understudied outcomes data across a full range of years from pre-donation through late-term post-donation.

All prospective donors at A2ALL-2 sites will be consented by a member of the A2ALL team located at those sites for general participation in A2ALL. The consent form will specify that, for the HRQOL Substudy, their contact information will be provided to the survey research center that will be calling them to conduct the telephone surveys. The study will utilize telephone-based survey methods to collect data at a total of 5 assessment time points across 2 years post-donation, with the surveys administered by survey research center personnel (see Section 6, Study Management). After the completion of each survey, each study participant will be paid $20. Such payments are required to maximize recruitment and retention and demonstrate appreciation for participants' efforts[69, 70].

4.3.7 Participant selection

All individuals approved as liver donor candidates and who are recruited for enrollment into A2ALL-2 will be eligible for this study.

After informed consent is obtained by staff at individual centers, all assessments will be conducted by telephone; no visits will be required. As noted above, respondents will complete a total of five assessments.

4.3.8 Data elements

Tables 2 and 3 below list the measures to be included in each of the telephone assessments. Table 2 includes measures for the pre-donation assessment, and Table 3 includes measures for the 3-month and 6-month post-donation assessments. (Subsequent assessments at 1-year and 2-years post-donation are identical to the earlier post-donation assessments except that the 10-item Posttraumatic Growth Inventory is included.) Our approach to the selection of specific instruments is identical to that employed for the long-term follow-up cohort, namely that measures were retained when possible (rather than replacing them with new measures of identical concepts and—where required—new measures are added to augment existing measures or assess domains not previously assessed).

874 **4.3.8.1 Table 2: HRQOL measures for prospective donor cohort, pre-donation**

Domain	Specific Items in Survey	Total No. of Items
Demographic items	63-68	6
Predonation factors/Risk factors		
• Simmons Psychosocial Background items (volunteer/donation history, importance of religion)	22-27	6
• Simmons Donation Decision-Making items/scales (decision process, ambivalence, others' influence, anticipated outcomes, black sheep donor)	1-13, 15-19, 30, 31, 50, 52, 57a-c, 58a-b, 59-61	30
• Simmons Preparedness for Donation item	62	1
• General QOL pressure to donate items	14	1
• Simmons Motivation for Donating Scale items	28a-k	11
Mental health		
• PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)[63]	54a-i, 55a-g, 56, 56a-e	11 to 22*
Somatic complaints		
• FACIT-Fatigue[64]	47a-m	13
• Brief Pain Inventory Short Form: numeric rating + activity impairment subscale[65]	46, 46a-g	1 to 8**
• Donation concerns about health and well-being (Simmons Concerns about Donation items, general physical item)	34, 48, 49, 51, 69	5
Interpersonal relationships		
• Relationship with Recipient items (Simmons items)	29a-d	4
• Simmons Family Support items	32, 33	2
Positive psychological status		
• Simmons Better Person scale items	20-21	2
• Campbell Global Life Satisfaction item	51	1
Generic HRQOL		
• SF-36v2	35, 36, 37a-j, 38a-d, 39a-c, 40-42, 43a-i, 44, 45a-d	36
Total No. of items/duration of assessment		130 to 148/** 23 to 29 min***

**depending on whether respondent skips out of sections
***estimate based on pilot testing

4.3.8.2 Table 3: HRQOL measures for prospective donor cohort, 3 months and 6 months post-donation

Domain	Specific Items in Survey	Total No. of Items
Demographic items	34, 41, 42, 56, 57	5
Mental health • PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)[63]	38a-i, 39a-g, 40, 40a-e	11 to 22**
Somatic complaints • FACIT-Fatigue[64] • Brief Pain Inventory Short Form: numeric rating + activity impairment subscale[65] • Post-Donation Symptom Checklist[20,25] • Post-Donation concerns about health (Simmons Worries about Donation items, Simmons Donation Stressfulness items; general QOL physical items)	 29a-m 28, 28a-g 27a-s 1, 9-15, 50, 51, 53, 58	 13 1 to 8** 19 12
Interpersonal relationships • Relationship with Recipient items (Simmons and general QOL items) • Simmons Family Support items • Simmons Worry about Recipient item • Toronto Recipient Behavior item • Simmons Preoccupation items • Simmons Grief items	 30, 32, 32e-j 33, 35 32d 32k 7, 31 32a-c	 2-14** 1-2** 1** 1** 2 4**
Financial concerns • Financial Burden of Donation items[28,66]	 43-47, 48a-d, 49	 10
Positive psychological outcomes • Simmons Better Person scale items • Simmons Satisfaction with donating items • Campbell Global Life Satisfaction item • Regret item from general QOL items • Posttraumatic Growth Inventory (10 items)[67]	 2-6, 36a-c, 54, 55 8a-g 37 52 Not asked at these time points	 10 7 1 1
Generic HRQOL • SF-36v2	 16, 17, 18a-j, 19a-d, 20a-c, 21-23, 24a-i, 25, 26a-d	 36
Total No. of items/duration of assessment		136 to 166/** 24 to 38 min***

**depending on whether respondent skips out of sections
***estimate based on pilot testing

For the prospective donor cohort HRQOL studies at 1 year and 2 years post-donation, the assessments are identical to those at 3 months and 6 months in the prospective cohort, except that the 10-item Posttraumatic Growth Inventory is included. This will increase the estimate time to 26 to 40 minutes.

4.3.9 Sample size and power calculations

We anticipate a total sample size of 375 liver donors. This sample size estimate is based on the numbers of living liver donor transplants performed at A2ALL-2 sites during the past 3 years and the expectation that we would enroll subjects for a total of two years going forward (allowing for follow-up of the last subjects enrolled before the end of A2ALL-2 funding). It also assumes 20% to 30% of prospective donors will refuse to enroll. Finally, across the study period, we assume that attrition will range between 10% to 15% (based on our past experience with donor and other transplant-related samples using the type of survey strategies proposed). Thus, by the final assessment wave, we expect to have a sample of 319 to 337 liver donors.

Given expected refusals to enroll and expected attrition, even with 319 liver donors (the worst-case scenario) we would have power exceeding .995 to detect small differences of less than 4% between a "case" rate of problems in a given HRQOL domain (e.g., rate of clinically significant psychiatric symptomatology) and a population/normative rate (Primary Aim 2, Objectives b.1. and b.2.). For Objective b.3., we would utilize the same strategies as those described for the long-term follow-up cohort. With a sample of 319, utilizing a regression approach to examine donor outcome status at a given time point (see also Section 4.3.10 below), with two-tailed alpha at .05, as many as 8 covariates controlled, and allowing the covariates themselves to have moderate-sized associations with the outcome, then our power to detect even conventionally small[68] differences in proportions or means will exceed .80. We note that we will not restrict our analyses to consideration of outcomes at only individual time points but will also utilize a mixed effects approach (which is appropriate both for interval and discrete outcomes). Power will be even greater under a mixed effect approach because such models allow for the inclusion of cases with incomplete data, and thus our effective sample size will be the total cohort enrolled. Therefore, even if we apply corrections for multiple comparisons (given the fact that we will examine multiple domains of HRQOL), our power will continue to exceed .80 for examining risk factor-outcome associations.

4.3.10 Statistical analysis

Similar to the long-term follow-up cohort, a chief aim of the analyses is to provide descriptive information about the new prospective cohort at each assessment time point post donation (Objectives b.1. and b.2.). Standard approaches to examine distributions of responses to survey measures will be examined (e.g., descriptive statistics, box plots, histograms). To examine prevalence of poor HRQOL outcomes in each identified domain, we will calculate the percentage of the sample at each time point that report clinically significant difficulties within a given domain. These rates, as well as mean scores on continuous measures, can be compared to norms for the measures.

To examine temporal patterns over time, we will use both survival analysis and mixed effects strategies. We will examine time to specific outcomes (e.g., onset of specific mental health problems) via survival analysis. We will examine temporal patterns of responses in each outcome domain with mixed effects models. We will evaluate assumptions regarding missing data patterns

and mechanisms and engage in sensitivity analyses to test the stability of our models. To examine risk factors for poor outcomes in the identified domains at (or by) a particular time point post-donation, we will initially utilize regression-based strategies (linear, logistic, or Cox proportional hazard, depending on the outcome measure of interest) (Objective b.3.). We will also apply mixed effects models to examine risk factors in relation to the trajectory of change in a given HRQOL outcome over time.

4.4 Primary Aim 4: To study the effects of pressure and flow on the outcomes of LDLT

4.4.1 Study Methods:

Baseline assessment will include the standard clinical and demographics required for the Core Protocol. Donor and recipient height, weight, and BMI will be recorded to normalize graft size and the extent of resection. Special attention will be paid to recipient parameters associated with the presence of portal hypertension including ascites and varices. Baseline recipient cross-sectional imaging will define liver and spleen volumes.

Standard surgical techniques will be used for the donor and recipient operations. Right lobe, left lobe, or left lateral segment donation and transplantation will be performed based on clinical parameters for graft selection.

The following will be recorded for donors: duration of surgery, hemodynamics, blood, and fluid replacement. Liver biopsy will be obtained at baseline and after parenchymal transection before devascularization of the graft. The liver graft will be weighed upon extraction. Donor pressure and flow measurements were collected as part of the A2ALL Core protocol, V1.9. We sought to define the values and variability of these observations in healthy livers. The value of these data was weighed against the intrusiveness of the probe insertion and portal vein puncture. From the outset we planned interim analyses with the expectation that we would stop collecting donor data after an adequate sample of reliable data was collected. The Surgical Innovations Committee met in Nov. 2011 and determined that the amount and quality of data was inadequate and donor collection should continue. A follow-up review was conducted on April 16, 2012 with data on 90 subjects. Key values were reviewed and deemed satisfactory for the purposes of the study and the Committee recommended that further data collection be suspended in the interest of donor safety. This was supported unanimously by the Steering Committee the following day and collection has been suspended.

The following will be recorded for recipients: duration of surgery, hemodynamics, blood, and fluid replacement. Anatomical details of the reconstructions will be recorded. Portal flow and pressure and arterial flow will be measured at the completion of the dissection. Central Venous Pressure (CVP), cardiac index, and mean arterial pressure (MAP) will be recorded. After revascularization of the graft, pressures and flows will be measured. CVP, cardiac index, and MAP will be recorded. A liver biopsy will be collected on the back table before implantation of the graft and after revascularization of the graft. The appropriate cutoff values for portal vein flow modulation have not yet been established. In the current protocol, center-based clinical preference will be the basis for flow intervention. If the recipient meets local criteria for portal flow modulation, pressure and flow measurements will be repeated after completion of each portal flow modulation and the type(s) of surgical and/or medical portal flow modulation(s) will be recorded.

4.4.2 Participant selection

All potential subjects will be presented with information and approached for consent.

4.4.2.1 Inclusion Criteria

- Recipients
  - Age 18 or older at the time of consent
  - Has had a living donor identified and accepted and LDLT is planned
  - Informed consent obtained
  - Is listed for single organ (liver) transplantation
- Donors
  - Age 18 or older at the time of consent
  - Has undergone donor evaluation process and was accepted and donation surgery is planned
  - Informed consent obtained

4.4.2.2 Exclusion criteria

  - None

4.4.3 Data elements

In addition to the data elements listed in Section 4.1.3, the following additional data will be collected:

- **Recipients**
  - Pre-operative imaging studies for measurement of liver and spleen volume
  - Intraoperative data
    - Portal pressure and flow measurements
    - Hepatic artery pressure and flow measurements
    - CVP
    - Mean arterial pressure
    - Cardiac output
  - Early postoperative period – Weeks 1 and 2, Month 1 -
    - Portal vein peak systolic flow velocity via Doppler on Day 1
    - Encephalopathy grade
  - Drain output
  - Liver MRI/CT at Month 3 for measurement of liver and spleen volume
- **Donors**
  - Pre-operative imaging studies for measurement of liver and spleen volume

4.4.4 Sample size and power calculations

We anticipate enrollment to average 10 recipients annually per site with a potential enrollment of 180 recipients over a 2-year period. This sample size estimate is based on the numbers of living liver donor transplants performed at A2ALL-2 sites during the past 3 years and the expectation that we would enroll subjects for a total of two years going forward (allowing for follow-up of the last subjects enrolled before the end of A2ALL-2 funding). It also assumes 20% to 30% of prospective recipients will refuse to enroll. Statistical analysis

The chief aim of the analyses is to provide descriptive information about relation between hepatic hemodynamics and graft size and functional outcomes. Standard approaches to examine distributions (e.g., descriptive statistics, box plots, histograms). We will attempt to identify correlations using regression analysis. Categorical comparisons between graft types will be examined to detect the effect of left lobe grafting.

4.5 Primary Aim 5: To compare the long-term histological outcomes in recipients of LDLT and DDLT with recurrent HCV infection

4.5.1 Study methods

The primary focus of this aim is to compare long-term outcomes (cirrhosis) of HCV recurrence in recipients of DDLT vs. LDLT. All participants from the Cohort A2ALL-1 study, including those whose donor was evaluated during the Retrospective era, will be eligible for inclusion. LDLT and DDLT recipients from the new A2ALL sites will be eligible if they had at least one potential donor present to the transplant center for evaluation, as per the original A2ALL-1 inclusion criteria. For these patients identified by the new sites, a waiver of consent for data extraction will be sought from their respective IRBs. for chart review if the patient is deceased or no longer followed. Subjects who received a transplant during the GAP era and meet the inclusion criteria will also be approached for consent or have their data collected under a Waiver of Consent as described above.

With the goal of focusing on longer-term outcomes, surviving non-retransplanted recipients (LDLT and DDLT) will return to their transplant center at least 3 years post-LT for a comprehensive evaluation, including collection of blood for DNA (if not already collected as part of Aim 2) and serum/plasma and liver biopsy. Retrospective data will be retrieved from all recipients, including those who undergo the protocol biopsy, those who are not biopsied because they are already deceased, have clinically decompensated cirrhosis, had been re-transplanted, refused biopsy, had a biopsy in the previous 12 months, have cirrhosis on a previous biopsy, or have a documented post-transplant Sustained Virologic Response (SVR). For deaths and re-transplants, the data up to the time of death or re-transplant will be collected. Clinical data, completed for all HCV patients, will be verified by the site hepatologist if recent biopsy data are not available.

Liver biopsies will be used for assessment of advanced disease and/or cirrhosis due to HCV recurrence. For recipients from the continuing A2ALL centers, demographic and clinical data will be collected as indicated in Section 4.1.3. For recipients from new A2ALL centers, a limited set of demographic and clinical data will be collected for Aim 5 only. For recipients from all A2ALL centers, data from previous liver biopsies documenting progression to cirrhosis or not will be collected – date of first biopsy documenting cirrhosis (for those who have cirrhosis) and date and fibrosis score of last biopsy documenting no cirrhosis (for all patients with and without cirrhosis).

The primary outcome of interest is the development of cirrhosis, defined by Ishak fibrosis stage ≥ 5 based on histology, or liver stiffness >12.5 kPa by transient elastography, or advanced HCV disease based on clinical criteria.
Liver biopsies will be obtained by the transjugular or percutaneous route (per site practice and PI discretion). In addition to unstained slides, additional slides will be stained with hematoxylin/eosin and trichrome. The Ishak scoring system will be used for staging of fibrosis to remain consistent with the central reading of A2ALL-1 biopsies. Inflammation, necrosis, steatosis, steatohepatitis and

evidence of fibrosing cholestatic hepatitis C (pericellular/sinusoidal fibrosis, cholestasis) will be assessed by the central pathologist. Concurrent conditions including acute and chronic rejection and histologic evidence of biliary disease will be noted. The central pathologist will also assess for biopsy adequacy by counting the number of complete portal triads present.

The central pathologist will also evaluate biopsy slides for those subjects who underwent a biopsy in the past 12 months, if that biopsy is serving as a surrogate for the protocol biopsy.

Recipients who met the endpoint of histological cirrhosis during the A2ALL-1 era will be included in this analysis. In order to verify concordance between the A2ALL-1 and A2ALL-2 central pathologists, all biopsies read by the A2ALL-1 pathologist will be re-read by the A2ALL-2 central pathologist. Similarly, biopsies performed during the A2ALL-1 era which were read locally as cirrhosis and the biopsy showing no cirrhosis immediately preceding that biopsy, that had not been reviewed centrally, will also be forwarded for re-read by the A2ALL-2 pathologist. For new A2ALL-2 sites, the latest liver biopsy from patients who do not undergo the ≥3 year protocol biopsy because they have already developed cirrhosis (either by clinical evidence and/or biopsy), the earliest biopsy read locally as cirrhosis, and the biopsy showing no cirrhosis immediately preceding that will also be re-read by the A2ALL-2 central pathologist.

Non-invasive assessment of fibrosis will be made for patients who refuse a biopsy or cannot have a biopsy due to safety concerns at UCSF, Toronto or Northwestern, or centers who acquire transient elastography equipment in the future. In addition, all patients who undergo biopsy at these centers will undergo transient elastography within 90 days of the liver biopsy for the purpose of validating liver stiffness with Ishak fibrosis score.

All subjects' clinical data will be reviewed by members of the HCV Sub-Committee for evidence of having met the clinical end-points of cirrhosis or advanced disease. The review will include assessment of the primary etiology of advanced disease (e.g., HCV disease or non-HCV factors including bile duct stricture, chronic rejection and vascular complications) or documentation of SVR after transplantation (based on undetectable HCV RNA at least 6 months after end of treatment).

4.5.2 Participant selection

In this study, we will recruit approximately 500 male and female HCV-infected adult liver transplant recipients from the 6 continuing A2ALL-1 centers (from those patients enrolled in the A2ALL-1 Cohort study), and from those concurrently transplanted at new A2ALL-2 centers (University of Toronto, University of Pittsburgh, Lahey Clinic).

In addition to those listed in Sections 4.1.2.1 and 4.1.2.2, the following inclusion and exclusion criteria apply to potential subjects with recurrent HCV.

4.5.2.1 Inclusion criteria

- Continuing centers will include LDLT and DDLT recipients enrolled in A2ALL-1 with evidence of HCV at transplantation.
- New centers will include transplanted patients (between January 1998 and August 31, 2010) who had at least one potential living donor who underwent an initial evaluation history and physical examination at the center and had evidence of HCV at transplantation.

- Recipients must have survived at least 90 days without retransplantation.

4.5.2.2 Exclusion criteria

- Documented SVR prior to transplant (non-detectable HCV RNA at least six months after end of treatment)
- Co-infection with hepatitis B virus (HBsAg-positive) before transplant
- Co-infection with HIV
- Receipt of a graft from an HCV-infected donor
- LDLT was one of the first 20 cases at the site

4.5.2.3 Subjects who will be approached for ≥3 year post-transplant liver biopsy

Surviving subjects who meet the inclusion criteria and none of the exclusion criteria listed in Sections 4.5.2.1 and 4.5.2.2 will be approached for a liver biopsy unless they have one of the following conditions: re-transplantation, clinical evidence of decompensated cirrhosis, cirrhosis documented on previous biopsy, liver biopsy performed within the past 12 months, or coagulopathy precluding a liver biopsy. Those subjects who had a biopsy in the past 12 months or had cirrhosis on a previous biopsy will have the biopsies re-read by the A2ALL-2 central pathologist.

4.5.2.4 Inclusion of deceased subjects, retransplanted subjects, and those who do not undergo the ≥3 year post-transplant liver biopsy

Inclusion of these subjects will be critical to avoid a survivor bias and also to meet the required sample size (Table 4). In order to collect the most robust representation of outcomes in LDLT and DDLT recipients, clinical information as well as liver histology data obtained post-transplant will be extracted. Data from recipients who are already deceased, are lost to follow-up, re-transplanted or have clinical evidence of graft failure will be collected retrospectively under a Waiver of Consent. Former Cohort subjects who have been re-transplanted and were ineligible for the main core protocol will be approached and consented for the HCV aim only. Those that are found to be deceased or lost-to-follow-up will have chart review conducted under a Waiver of Consent as described above. Gap-era Core subjects who had previously reached the endpoint of re-transplant will be approached for consent into the HCV sub-study so that their charts can be reviewed. If they are lost to follow-up, their charts will be reviewed under a Waiver of Consent as described above.[

4.5.3 Data elements

Since we have previously shown that center experience is an important determinant of outcome after LDLT for HCV, statistical analysis of outcome will adjust for center experience. New A2ALL sites will therefore identify those LDLT recipients done with center experience >20 cases.

In addition to the data elements listed in Section 4.1.3, the following additional data will be collected:

- **Living Donors (characteristics at donation)**
  - Age, race, gender, diabetes, BMI, relationship to recipient
- **Deceased Donors (characteristics at transplant)**
- Age, race, gender, diabetes, BMI, relationship to recipient, cause of death, donation after cardiac death (DCD) status

- **Recipients**
  - Labs (albumin, AST, ALT, bilirubin, creatinine, INR) at the time of transplant, diabetes, BMI, cold and warm ischemia times, treated acute rejection episodes (dates/treatment), CMV disease (dates/treatment), HCV treatment (dates, drug regimen, date of SVR if applicable), immunosuppression regimen at day 0-7, at 12 months post-transplant, and at time of biopsy, case number (for LDLTs).
  - Biosamples – collected once, at the time of liver biopsy or after activation into the HCV component of the study (> 3years post-txp) – serum, plasma, whole blood for DNA extraction (if not previously collected as part of Aim 2). These samples will be stored at the NIDDK Biosample Repository for future studies on HCV recurrence after liver transplantation.
- **Outcomes: Severity measures (with dates)**
  - Liver biopsy (Ishak score)
  - Measurement of liver stiffness by transient elastography
  - Graft survival: date and cause of graft loss, date of retransplant, explant pathology report, dates of development of complications of liver failure (ascites, encephalopathy, variceal bleeding)
  - Patient Survival: date and cause of death, autopsy report (if available)
  - Hepatic venous pressure gradient (mmHg), if available, as part of obtaining liver biopsy via the transjugular route, including free and wedged hepatic vein pressures[74,75]
  - Clinical Data: presence of ascites, hepatic encephalopathy, bleeding esophageal varices

4.5.3.1 Table 4: Schedule of data and biosamples for HCV study

Study Population	Data Collected	OLT Admission	post-OLT
1. A2ALL-1 Cohort Study enrollees*	Demographics	+	+
	Transplant data (e.g., CIT, WIT)	+	
	Outcomes		+
2. Concurrently transplanted DDLT recipients from New A2ALL-2 Sites** with ≥ 1 potential donor	Diabetes (medication-treated)	+	+
	Rejection/treatment		+
	CMV/treatment		+
	HCV treatment and response		+
	Biliary complications		+
	Immunosuppression	+	+
3. Concurrently transplanted LDLT recipients from New A2ALL-2 Sites**	Liver Biopsy		+
	Lab values	+	
	Serum		+
	Plasma		+
	Whole blood for DNA (if not previously collected for Aim 2)		+

*A2ALL-1 Sites continuing in A2ALL-2 Study: Columbia University, University of Colorado, Virginia Commonwealth University, Northwestern University, University of Pennsylvania, University of California at San Francisco

** Patients transplanted during the A2ALL-1 Era from New A2ALL-2 Sites: Lahey Clinic, University of Toronto, University of Pittsburgh.

4.5.4 Sample size and power calculations

All sample size calculations below assume a significance level of 0.05, two-sided testing, and an exponential distribution of times to cirrhosis. A clinically meaningful difference in risk of cirrhosis after a median follow-up of 5 years will be defined as ≥15%. The predicted proportion with cirrhosis (Ishak 5-6 or cholestatic hepatitis on biopsy, liver stiffness measurement ≥12.5 kPa by transient elastography, or clinical criteria of cirrhosis per HCV disease form) at 5 years for DDLT is estimated to be 5%. To detect a greater proportion in LDLT than DDLT (12% vs. 5%, hazard ratio=1.41) with 92% power will require a sample size of 200 per group. As depicted in Table 5, such a sample size should be reached by patients currently in Retro/Cohort A2ALL-1 with the participation of new A2ALL sites (Toronto, Lahey, Pittsburgh); we estimate that there are currently 221 DDLT recipients with at least one donor evaluated and more than 304 LDLT recipients currently alive and ≥ 3 years post-transplant. Inclusion of almost all DDLT recipients into the study will be needed to reach sample size, although any shortfall may be offset by the extra power gained by the likely occurrence of more than 200 LDLT enrollees.

4.5.4.1 Table 5: Number of LDLT and DDLT recipients from each study site known to be alive at least 3 years post-transplant from the A2ALL-1 Cohort Study (continuing sites) and the A2ALL-1 Cohort Study era (new sites)

	Columbia	NW	Penn	Colorado	Lahey	UCSF	Toronto	Pitt	VCU	Total
DDLT	16	4	3	21	14	29	112	21	10	221
LDLT*	44	13	6	31	60	20	70	44	27	304

*DDLT recipients are those who had at least one potential living donor evaluated.

4.5.5 Statistical analysis

The primary outcome is cirrhosis based on liver biopsy, or in cases without biopsy, based on transient elastography and clinical and laboratory criteria of advanced disease. In general, if information from more than one source is available, the order of preference of information is: biopsy, transient elastography, and clinical and laboratory criteria. The biopsy measures include fibrosis score (standardized to 6-point ordinal scale, 0-6), or cholestatic hepatitis (scored as 6), or advanced disease as determined from the HCV Disease Form (scored as 6).

Patients with a biopsy documenting cirrhosis will be considered to have met the primary endpoint at some time prior to biopsy (i.e., left-censored data). Those with a biopsy documenting no cirrhosis will not yet have crossed the threshold (i.e., right-censored data). If additional biopsies are available, then we may be able to isolate the interval in which cirrhosis occurred as between the last biopsy documenting no cirrhosis and the first biopsy documenting cirrhosis (interval-censored data). If biopsy is not available, liver stiffness measurement by transient elastography will be used to determine if primary endpoint of cirrhosis was met. In the absence of both biopsy and liver stiffness measurement, primary endpoint will be determined based on clinical and laboratory criteria contained in the data elements listed in Section 4.5.3. This information will also be used to determine if the primary endpoint was reached in patients who died or who had been re-transplanted. Data will be reviewed by the HCV Adjudication Committee to determine if criteria for cirrhosis were met and if death or graft loss was HCV-related. The cumulative distribution (or survival) function for time from transplant to cirrhosis will be estimated using either parametric models or nonparametric (Turnbull estimator) methods. To test for a difference in this distribution between

LDLT and DDLT, adjusting for covariates such as age and MELD score, parametric regression models (e.g., using SAS Proc Lifereg), or discrete survival analysis methods (e.g., using SAS Proc Genmod) will be used.

In addition, times to patient death and graft failure will be analyzed as right-censored outcomes, using standard survival methods (Kaplan-Meier estimates, log rank tests, and Cox regression). Non-Markov multistate models[73] will be considered if feasible with the available data.

Validation of transient elastography will be performed based on the subset of patient who undergo both transient elastography and biopsy within 90 days of each other. The correlation coefficient between transient elastography measure and Ishak score from biopsy will be calculated. A calibration model will be fit to convert transient elastography values into Ishak equivalents. A strong correlation (e.g., 0.7 or higher) would be expected if the two methods are to be considered interchangeable. A transient elastography cutpoint of values above 12.5 kPa are indicative of cirrhosis.

4.6 Primary Aim 6: To understand the history of pain management and to measure quality of care in pain control in living donors following partial hepatectomy.

4.6.1 Study Methods

The study uses two surveys to collect information about live donor pain management. The first survey collects information from care providers in the A2ALL Consortium regarding the details of their choice of pain management and their opinions/beliefs.

4.6.1.1 Study Methods – Retrospective Component

We used the APS-POQ-R as a template to develop the survey questions. The survey addresses aspects of practice that are linked to outcome, including: resources and personnel participating in pain management, methods used to assess pain, and opinions about the efficacy of pain management. An electronic retrospective survey (see Appendix E) will be distributed to the transplant research coordinator and completed by a surgeon, nurse and anesthesiologist (if the latter is involved in pain management) at each of the nine A2ALL clinical centers. The survey measures the methods and personnel used in postoperative pain management, how pain was assessed and what quality indicators were used assess performance. Data will be collected via a commercial web-based survey application .

4.6.1.2 Study Methods – Prospective Component

All sites will utilize the APOS-POQ-R (see Appendix F) to collect information about the outcome of pain management from the post-op liver donors' perspective. A study coordinator will read the questions to the subjects and record their answers 48 hours following liver donation surgery. A database will be constructed from the subjects' answers to the APS-POQ-R that is not biased by the source of the data or the technique used for pain management. Data will be analyzed for overall effect by measuring patient satisfaction (how living donors rate the quality of their pain care). Answers to the survey questions assess overall patient satisfaction. The responses to individual questions that identify specific areas of pain management also relate to patient satisfaction.

Collection and analysis of this data corresponds to our study's objectives summarized in Section 3.6.1.

4.6.1.3 Participant Selection – Retrospective Component

The lead investigator at each site will select up to three health care providers involved in post liver donation pain management: a liver transplant surgeon, an anesthesiologist, and the nurse transplant coordinator.

4.6.1.4 Participant Selection – Prospective Component

Inclusion Criteria

- Adult living liver donors

Exclusion Criteria

- History of chronic pain
- History of narcotic use (routine scheduled narcotic use for treatment of a pain disorder diagnosed and treated by a physician)
- Medically unstable at 48 hours post-donation surgery
- Language barrier

4.6.1.5 Data elements

Retrospective Component:

- Responses to retrospective survey (see Appendix E)

Prospective Component

- Demographic information as described in Section 4.1.3
- Intraoperative, perioperative and post-operative complication and hospitalization information as described in Section 4.1.3
- Responses to screening questions regarding history of chronic pain and narcotic use
- Responses to the APS-POQ-R survey (see Appendix F)

4.6.1.6 Sample size and power calculations

Retrospective Component: The unit of analysis is the clinical center, with a sample size of 9. This analysis will describe clinical practice at the 9 A2ALL centers and will not attempt to make inference to a larger population.

Prospective Component: We anticipate that approximately 200 future donors will be enrolled in A2ALL-2. Although it is unlikely that more than 200 donors will be accrued, enrollment will remain open during A2ALL-2 to allow as much power as possible to assess center effects and variables predictive of satisfaction with pain management. Because many of the study measures will be presented descriptively, we first give the confidence interval (CI) width for, e.g., the true mean satisfaction score (0-10 scale) assuming a standard deviation of 2.0. With n=200, we will have 93% probability that the width of this CI will be no greater than +/- 0.30. For comparing the satisfaction scores at two of the 9 centers, say each with n=30 donors, we will have 90% power to detect a difference in means of 1.7. Sample size calculations were made using the SAS Power procedure (SAS Institute, Inc., Cary, NC).

4.6.1.7 Statistical Analysis

Retrospective Component:
The methods and personnel that each center uses to manage postoperative pain in live liver donors and methods they have stopped using, will be presented using descriptive statistics. If possible, graphical methods will be used to display the changes over time.

The medical specialty of care providers responsible for pain management and assessment will also be described for the 9 A2ALL centers. This summary will include both the type of specialists involved, and whether pain management involved an Acute Pain Team or not. Both the proportion of centers with Acute Pain Teams and the composition of these teams will be described. The continuity of pain management through phases of patient locations (e.g., ICU, surgical ward) will also be reported. Finally, the opinion of the medical care providers on the adequacy of pain control at their center will be described, and will also be compared to patient reports at that center (using data from prospective component of the study).

Prospective Component:
Satisfaction will be assessed using (a) the single question (P9), measuring overall satisfaction, and (b) the individual items of the pain questionnaire (P1-P8 and P10-12). These outcomes will be presented using descriptive statistics, including frequencies, means and standard deviations. Histograms and/or boxplots will be used to identify the forms of the distributions and to identify outliers. Aspects of care with low scores or a large standard deviation will be identified as practices that require overall improvement. Boxplots and analysis of variance will also be used to display and compare quality indicators from the APS-POQ-R measures by center.

To identify aspects of care that account for differences in patient satisfaction, we will evaluate predictors of overall satisfaction (P9) using linear regression. Predictors of overall satisfaction to be tested will include the pain relief variables (P1-P7), participation in decisions about pain treatment (P8), helpfulness of information received (P10), non-medicine methods of treatment (P11, P12), demographic variables, and donor relationship.

The complications outcomes (P6) will be analyzed using descriptive statistics as described above. Pain questionnaire data will also be linked to A2ALL-2 donor complication data to assess whether aspects of the donor pain experience, based on questions from the APS-POQ-R, are predictive of subsequent complications.

5 Human Subjects

5.1 Protection of human subjects

5.1.1 Institutional review board

This study and analysis will be performed under Institutional Review Board (IRB) oversight. Prior to the initiation of the study, an IRB approval for study of human subjects will be obtained separately from the IRB of each of the participating transplant centers and the DCC. Revisions to the study protocol and changes in the study design will also be submitted to the individual IRBs for approval prior to implementation.

Subjects will be enrolled in the core protocol with full informed consent which will include the gathering of privileged health information (PHI), the collection of blood and tissue specimens beyond that normally performed for transplant/donation clinical care as well as samples for genetic studies, and the collection of medical and quality of life information at defined intervals prior to and after the transplant in donors and recipients.

Each participating center will be responsible for obtaining such human subjects research authorization and will create an informed consent document detailing the procedures described above in the language required by their respective institutes. All key personnel at the participating centers will have successfully completed their IRB-required training and certification for human subject's research and HIPAA researchers' privacy requirements.

5.1.2 Patient confidentiality

5.1.2.1 Core Protocol

Special procedures for ensuring patient confidentiality will be implemented. Data transmission and the distributed data systems have multiple layers of security as discussed below in Section 6, Study Management. Each study subject will be assigned an identification number. Only this number will be used to identify subjects in any individual tabulation. The PHI that is collected will represent the minimum necessary to successfully execute the study. The DCC plans to periodically update outcomes and mortality information (graft failure, liver failure, mortality) in the study population by linking to the Scientific Registry of Transplant Recipients (SRTR). The DCC maintains a Data Use Agreement with the SRTR's contractor and adheres to the requirements set forth to protect subjects' privacy and confidentiality. Links to the SRTR database will be destroyed when the study has ended.

PHI entered into the database at the site level will only be visible to study personnel accessed through a triple password regimen. The PHI is encrypted at the site level. Site personnel have the decryption key, and it is not available to the DCC. It is expected that only group data will be published. If individual subject data are to be published, no identifying information will be included. The study files will be maintained in a secure location as described above. Access to computerized data will be restricted to study personnel. Password authorization will be enforced. Previous use of this security system and secured server indicates that this technique is very successful in assuring the protection of confidential information.

Authorized representatives of the Sponsor, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), participating clinical institution, DCC monitoring staff, as well as the IRB, have access to medical records and records from participation in this study. Such access is necessary to ensure the accuracy of the findings.

5.1.2.2 HRQOL Substudy

Potential risks of the HRQOL substudies include a possible breach of confidentiality. Care will be taken at all stages of the protocol to ensure and protect study participants' confidentiality. Individual A2ALL sites will each assure, and their consent forms will explain, that the living donor transplant team and program will not be informed as to the contents of any completed HRQOL assessment instruments by study participants. No materials gathered during the research will become part of

participants' medical records, including any records maintained by the living donor programs. No individual participant will be identified in any published report. Data collected during the research will be entered into password-secured databases by research staff authorized by the survey center PIs at Northwestern University (NWU) and the University of Pittsburgh (Pitt) to do this (see Section 6, Study Management, for further discussion of survey research center management issues). Research records and documents will be kept in a locked file. No research documents will contain the names of study participants. Instead, identification numbers will be assigned to each study participant to mask their identity, and the list linking participant names and IDs will be stored in a separate locked file in the survey center PI's office. The study interviewers at the centralized survey research centers, who will perform HRQOL study assessments, will have study participant contact information but they will not be employed by the living donor programs and they will all sign a statement indicating that they will abide by HIPAA and IRB confidentiality regulations.

5.1.3 Risks to the study participant and adequacy of protection against risk

Patients enrolled in this study will experience more than the normal amount of testing which is customary for this complicated medical and surgical procedure. Additional time will be required both before and after the transplant for the gathering of medical and quality of life information. Blood and liver tissue will be collected and stored for special tests which are not normally required for clinical care. Venipuncture carries risks of pain and bruising at the puncture site. Intraoperative biopsy carries the risk of increased bleeding. Percutaneous liver biopsy carries the risks of: pain (20%), severe bleeding requiring a blood transfusion or an operation to stop the bleeding, infection, puncture of the gallbladder, lung or kidney (~1 per thousand), and death (~1 per 10,000). In addition to the risks associated with a percutaneous liver biopsy, a liver transjugular liver biopsy carries the following risks: collection of hemotoma in the neck, temporary problems with the facial nerves, and temporary voice problems. Portal and hepatic vein pressure and flow measurement also carries the risk of bleeding and damage to the vein(s). All research procedures will be carried out by qualified personnel who are experienced in performing the tasks.

The study participant interviews and the HRQOL instruments do not involve any known physical risks. Individuals may experience psychological discomfort in answering repeated, longitudinal assessment questions related to their emotional well-being, health concerns and worries, relationship problems, or financial hardships. With respect to potential discomfort developing during interviewing, we note that the interviewers will be trained by the investigators to be sensitive to participant discomfort and concerns. Regarding the post-donation assessments in particular, we have found in our previous studies involving living donors that they often report that, rather than being stressful, post-donation assessments are a source of support to them and that they are glad to have had the chance to discuss the donation experience and post-donation issues. There is a potential risk of breach of confidentiality that is inherent in all research protocols and steps to minimize this risk are described above. Steps to minimize risk and address any psychological discomfort are addressed below.

> Recruitment and Informed Consent. At each A2ALL site, individuals eligible for study (based on criteria described in Section 4.1.2 above) will be approached by a member of the living donor transplant team for release of their protected health information and contact information so that study staff may approach them to describe the study and obtain informed consent. All consent forms will be HIPAA compliant. A copy of the signed consent forms

will be kept by the study participant, and one will be kept in the research records at the site where the participant was enrolled. Participants will be informed verbally and in the informed consent form that their contact information will be released to a centralized survey research center which will contact them and conduct the interviews by telephone. They will be informed of the assessment time points and the payments they will receive for participating in the HRQOL assessments.

Psychological discomfort during study procedures (i.e., during study assessments). With regard to participants' psychological discomfort and overall well-being, we noted above that the interviewers will be specifically trained to be sensitive to subjects discomfort and concerns. These issues will be of central focus during their training. If a participant finds the research procedures to be upsetting or aversive, he/she will have the option to withdraw from the study. We will refer participants to an appropriate clinical setting for evaluation and/or treatment (a) in the unlikely event that an interviewer judges a participant to immediately require such care for psychological distress, or (b) if the participant him- or herself inquires about receiving such care. The criteria for establishing that a participant immediately requires care are that the participant expresses thoughts or an intention to harm him/herself or others. During the HRQOL assessment interviewers will be alert for any statements volunteered by the participant regarding thoughts or intent for harm or for the participant's affirmative response to the PRIME-MD items that refer to thoughts or intent of harming self or others. In this situation, confidentiality would have to be broken in order to protect the participant. The participant will be made aware of this contingency in the informed consent form. If this circumstance arises, the interviewer will initially consult the specific center study coordinator to arrange for an evaluation at the respective institute, or at a local facility in the geographical area where the participant resides if he/she lives a long distance from the living donor transplant program and prefers a local referral. This approach meets IRB guidelines, and these procedures have successfully facilitated such local and long-distance arrangements in our past studies. We have had to invoke these procedures with any transplant-related population extremely rarely.

5.1.4 Unauthorized data release

5.1.4.1 Core Protocol

The data sets will be stored on a secure server with restricted access (requires a unique username and password) at the DCC and every precaution will be taken to keep the information private. However, there is always the possibility of unauthorized release of data about subjects. Such disclosure would be extremely unlikely to involve a threat to life, health, or safety, since the only PHI that will be collected is month and year of birth. It is conceivable that such disclosure could have psychological, social, or legal effects on the patient. Using the standard security procedures (described above under patient confidentiality) can effectively minimize the risk of unauthorized disclosure of data. All study personnel who have access to patient data will be educated regarding the need to protect confidentiality and the procedures to be followed to ensure such protection. All staff will also be required to sign a standard medical record confidentiality agreement. The computer system on which data are maintained uses standard password protection procedures to limit access to authorized users.

5.1.4.2 HRQOL Substudy

The protection of study participant privacy is especially important as it relates to access and transmission of research data. We will take the following steps to assure the confidentiality of research data during storage and transmission via the internet. First, participants' names and identifying information will not be transmitted with study assessment information. Instead, an identification number will be used for data transmittal. Secondly for the handling and transmittal of data, the centralized survey research centers will provide computer and web page security and data transmission between their web servers to World Wide Web users and thus provide secure transmission of data to the DCC (using such protections as Secure Sockets Layer (SSL), SSL Certificate authentication, data encryption and password protection). Each individual needing to access the web sites will be provided with a unique Username and a Password.

At the survey research center responsible for data collection from a given participant, only the PI and authorized study staff will be allowed access to participant information and all computerized data will be password protected. In addition, the center will monitor individuals who are accessing participant information to assure that strict authorized access only is maintained. At the individual A2ALL sites responsible for enrolling study participants, similar procedures will be used to ensure that informed consent forms are maintained (e.g., locked files accessible only to authorized study staff).

5.1.5 Adverse event monitoring and reporting

5.1.5.1 Definition of adverse event

An adverse event (AE) is any untoward medical occurrence or unfavorable and unintended sign in a research subject that occurs during or as a result of a research procedure.

For this observational study, the majority of the procedures are standard clinical care and adverse effects of clinical care will be tracked as complications but will not be considered adverse study events. Each center will review the list of study procedures and identify the specific procedures that are not standard-of-care at their institution and these will be considered research procedures. Complications that are a result of research procedures will be reported and tracked as adverse events.

5.1.5.2 Assessment of event severity and relationship to treatment

The modified World Health Organization (WHO) grading system will be used for grading severity of AEs (Appendix C). For AEs not covered by the modified WHO grading system, the following definitions will be used:

Mild:	awareness of sign, symptom, or event, but easily tolerated
Moderate:	discomfort enough to cause interference with usual activity and may warrant intervention
Severe:	incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention

Life-threatening:	immediate risk of death

The investigator must also assess the relationship of any adverse event to the research procedure, based on available information, using the following guidelines:

Unlikely related:	no temporal association, or the cause of the event has been identified; or the procedure cannot be implicated
Possibly related:	temporal association, but other etiologies are likely to be the cause; however, involvement of the procedure cannot be excluded
Probably related:	temporal association; other etiologies are possible, but unlikely

5.1.5.3 Definition of serious adverse events

A serious adverse event (SAE) is any adverse experience that results in any of the following outcomes:

- Death;
- Life-threatening AE (i.e., one that places the subject, in the view of the investigator, at immediate risk of death from the AE as it occurs);
- Persistent or significant disability/incapacity;
- Required in-patient hospitalization, or prolonged hospitalization;
- Congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, if based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.1.5.4 Reporting responsibility

All adverse events must be recorded. The onset and end dates, severity and relationship to study procedure(s) will be recorded for each adverse event. Any action or outcome (e.g., hospitalization, additional therapy, etc.) will also be recorded for each adverse event. Subjects will be questioned and/or examined by the investigator or his/her designee for evidence of adverse events.

All AEs and SAEs must be reported by the investigator to the A2ALL Data Coordinating Center (DCC). The DCC will review reports of all related SAEs and other relevant information immediately, and may request additional information from sites for analysis of these events. Sites will report serious adverse events according to the time frames outlined below.

All events that are serious and related (possibly or probably) must be reported to the DCC within 24 hours of the investigator being informed of the event. Follow-up information about a previously reported serious and related adverse event may be reported to the DCC within 7 working days of the investigator receiving the information; however, important follow-up information must be submitted

within 24 hours. All deaths connected to a study procedure must be reported to the DCC within 24 hours of the investigator being informed of the event.

5.2 Benefits to the patients

There are no direct benefits to the patients for participation in the study.

5.3 Inclusion of women

This is a multi-center study drawing on a clinical population from nine transplant institutions across the United States and Canada. The demographics of the study population are pre-determined due to the all-inclusive nature of the study. Women will be included in the study as living liver donors or as recipients. It is anticipated that the representation of women will correspond to the fraction of females in the living liver donor and recipient population.

5.4 Inclusion of minorities

This is a multi-center study drawing on a clinical population from nine transplant institutions across the United States and Canada. The demographics of the study population are pre-determined due to the all-inclusive nature of the study. Racial and ethnic minority groups will be included in the donor and recipient components of the study and will be proportional to their representation in the living liver donor and recipient population.

5.5 Inclusion of children

The study specifically excludes children. By definition this study is designed to examine the risks, benefits and outcomes of Adult-to-Adult living donor liver transplantation. However, eligible subjects between the age of 18 and 21 years will be enrolled.

5.6 Data and safety monitoring plan

Accepted principles of data and safety monitoring will be observed throughout the conduct of the A2ALL study. The NIH will appoint an independent Data Safety and Monitoring Board (DSMB) that will provide study oversight. The DSMB will approve the study protocol prior to enrollment and will also approve all subsequent protocol revisions.

Each transplant center principal investigator will be responsible for monitoring the enrollment of subjects and submission of data to the DCC. The DCC will be responsible for monitoring for effective conduct of the protocol and accurate and timely data submission.

IRBs will be provided feedback on a regular basis.

Training of study coordinators and study monitoring activities will be conducted by the DCC to ensure patient confidentiality and privacy and to maximize the reliability, accuracy, and timeliness of study data.

The HRQOL substudy committee and relevant survey research center staff will conduct quarterly meetings to review recruitment/enrollment progress, data collection activities, review participant complaints and any adverse events (see adverse event procedures above). As a part of these meetings the centralized survey research centers will generate quarterly reports to the HRQOL

substudy committee on the tracking and management of all substudy participants. In particular, the centralized survey research centers report monthly retention rates, outstanding interviews/surveys, and data entry progress. The centers will use electronic tracking systems to monitor numbers of interviews scheduled, completed, refused, pending, etc. Data will be routinely exported from the system, examined for accuracy and completeness, and backed up to secure storage devices. Upon completion of data collection, final processing and cleaning of data will be conducted. A technical report detailing specific project methodology, response rates, and other details will be produced. The HRQOL substudy committee will supervise these activities and provide additional assistance as may be required.

5.7 Study organization

5.7.1 Clinical transplant centers

The participating Clinical Centers will have primary responsibility for developing the study protocol, maintaining high rates of follow-up and data collection, obtaining data of high quality, and interpreting, presenting, and publishing findings from the study.

Columbia University Medical Center
New York, NY
Principal Investigator: Jean Emond, MD (Steering Committee Co-Chair)

Northwestern University
Chicago, IL
Principal Investigator: Michael Abecassis, MD

University of Pennsylvania
Philadelphia, PA
Principal Investigator: Kim Olthoff, MD

University of Colorado Denver
Aurora, CO
Principal Investigator: James Burton, MD

University of California, San Francisco
San Francisco, CA
Principal Investigator: Christopher Freise, MD

Virginia Commonwealth University – Medical College of Virginia
Richmond, VA
Principal Investigator: Robert Fisher, MD

Lahey Clinic
Burlington, MA
Principal Investigator: Elizabeth Pomfret, MD

University of Pittsburgh Medical Center
Pittsburgh, PA
Principal Investigator: Abhinav Humar, MD

University of Toronto
Toronto, Canada
Principal Investigator: David Grant, MD

5.7.2 Data coordinating center

The Data Coordinating Center (DCC) contributes content area expertise and shares in scientific leadership of the research group. The DCC has developed a communication infrastructure that includes meetings, teleconferences, electronic mail and bulletins, interactive web-based encounters and written correspondence. The DCC assists in protocol development and preparation of scientific publications. The DCC has the major responsibility of creating a database and data collection systems for the transplant centers, ongoing evaluation of data quality and performance monitoring of the transplant centers and statistical analyses of the data. The DCC will also create a comprehensive Manual of Operations (MOO) that will govern the conduct of the study. The manual will detail the protocols, protocol clarifications and amendments, summary of the regulatory requirements for the study, instructions for enrollment, data collection, data management, visit schedules and detailed instructions on the use of the electronic data submission. The DCC is responsible for clinical monitoring of the study.

University of Michigan
Ann Arbor, MI
Principal Investigator: Robert M. Merion, MD (Steering Committee Chair)

5.7.3 Steering committee

The primary governing body of the study is the Steering Committee, comprised of each of the Principal Investigators of the transplant centers, the Principal Investigator of the DCC and the NIDDK Project Officers. The Steering Committee develops policies for the study pertaining to access to patient data and specimens, ancillary studies, performance standards, and publications and presentations. They develop the study protocol and meet to discuss the progress of the study and to consider problems arising during its conduct. The Steering Committee may establish subcommittees to further develop specific components of the study protocol and propose ancillary areas of study. Small working groups may be established to prepare manuscripts and presentations.

5.7.3.1 Workgroups and subcommittees

The following subcommittees have been established to address specific issues, develop protocols and provide administrative guidance to the project:

- Protocol Design
- Hepatitis C Virus (HCV) Workgroup
- Hepatocellular Carcinoma (HCC) Workgroup
- Regeneration and Function Workgroup
- HRQOL Workgroup
- Surgical Innovations Workgroup

- Publications Committee
- Ancillary Studies Committee

6 Study Management

6.1 Data collection, case report forms, and data entry: Aims 1, 2, 4, and 5

The DCC will utilize the web-based *A2ALL-Link* as the data management nucleus for the A2ALL-2 studies. *A2ALL-Link* is a database platform developed by Arbor Research Collaborative for Health (Arbor Research). The research team at Arbor Research has successfully collaborated with the University of Michigan DCC team on another NIH-sponsored study researching outcomes of living kidney and lung donors. *A2ALL-Link* provides many improvements over the database application employed during the first iteration of the A2ALL study.

The DCC will utilize the *A2ALL-Link* to create electronic case report forms to capture all relevant study data for the core study and all investigational/research protocols that are developed and implemented during the course of A2ALL-2. The *A2ALL-Link* system allows real-time monitoring of study data for protocol adherence, quality assurance, adverse event reporting, discrepancy reporting, and other trends.

The DCC plans to periodically update outcomes and mortality information (graft failure, liver failure, mortality) in the study population by linking to the SRTR. The DCC maintains a Data Use Agreement with the SRTR contractor and adheres to the requirements set forth to protect subjects' privacy and confidentiality. Links to the SRTR database will be destroyed when the study has ended.

6.2 Data collection, case report forms, and data entry: HRQOL Substudy

For the HRQOL Substudy, data collection for both the long-term follow-up and the prospective cohort study will be accomplished through the involvement of the study's two survey research centers, with Northwestern (NWU) taking responsibility for continuing A2ALL sites (UCSF, NWU, VCU, Colorado, Columbia, Penn) and the University of Pittsburgh taking responsibility for the three new sites (Pittsburgh, Lahey, Toronto).

We will utilize telephone survey methods in order to collect the data because these methods are known to produce higher response rates than mailed questionnaires.[43,71,72]. To ensure uniformity, accuracy and consistency of data collection, we will employ training and monitoring of interviewers, and we will use computer assisted telephone interviews (CATI). Interviewers will be trained in general and project-specific interviewing techniques using a combination of didactic presentations, written handouts, video instruction, and hands-on experience. Interviewers will be continuously monitored during data collection for quality assurance, and periodic retraining sessions will occur as necessary. We will employ real-time data collection and entry through CATI. CATI systems involve survey instruments programmed into an electronic data system, interviewers reading the questions directly from the computer screen, and responses being directly entered into the database. This eliminates the need for independent data entry and minimizes transcription and coding errors. It is also cost-efficient.

6.3 Data management

All core study data will be entered into the electronic data entry system by study coordinators at each study site. These data will be encrypted and transferred to the DCC and stored on a secure server at the University of Michigan's subcontractor (Arbor Research). Access to the server and data entry system is limited and requires a unique username and password combination. The servers are backed up daily and physically stored in a locked facility.

For the HRQOL study, both the NWU and Pittsburgh survey research centers will provide secure transmission of electronic files containing all survey responses to the DCC. Both centers will institute electronic tracking systems to ensure that interviews are scheduled and completed in a timely manner and that data is efficiently transmitted to the DCC.

All analysis of the data sets will utilize de-identified (coded) data sets.

6.4 Quality control and database management

The first steps in ensuring protocol compliance are good protocol design and careful orientation of study personnel. Following final agreement on protocols, and prior to study initiation at any of the transplant centers, the DCC will organize a Training and Certification session for transplant center study coordinators/data entry personnel.

The electronic data entry system will have built-in data checks as part of study quality assurance. Protocol compliance will be assessed by monitoring the submission of data at required intervals. Data inconsistencies and discrepancy reports will be reviewed by the Clinical Monitors so that necessary queries can be generated and sent to the transplant center study sites for verification and resolution.

Periodic requests may be generated for the submission of random source documents to assess the quality of data acquisition and data entry at each site. In addition, the Clinical Monitor or Project Manager will visit each site at least once a year to review source documents, monitor regulatory compliance, and assess protocol adherence.

In addition to source document verification, the Clinical Monitor and Project Manager will produce reports from the database to look for inconsistencies in submitted data, particularly for repeated measures data elements, even if data do not fall outside of built-in validation routines.

Studies of intra-subject and inter-subject data variability by transplant center as well as intra-transplant center and inter-transplant center data variability will be used to further ascertain random or systematic data quality issues.

Comparisons of major endpoints from the current study to national data from the SRTR will be used to assess the extent to which participants in the A2ALL study are representative of the general population of patients undergoing these procedures in the United States.

6.5 Data security/data transfer

For the Core Protocol, personnel at each study center will collect and enter data into the web-based data entry system. The following data security contingencies are in place:

- Compliance with Industry Standards Regarding Data Security (HIPAA and 21 CFR Part 11)
- Audit trails are maintained for all activity and all changes to any data element
- All servers, web servers, firewalls, etc. are configured and maintained according to industry best practice guidelines for backup, security, continuity of operations, and protection of PHI
- All data are available only to authorized users from each site after secure login with encryption, with all site activity audited at the user level
- All transmissions between the Internet and the database are encrypted using a 128-bit encryption algorithm
- There is a comprehensive security plan in place

Detailed instructions on the use of the database platform, data element definitions and a code list will be provided in a Manual of Operations (MOO). Each study site will be provided a copy of the MOO and the entire manual will be available on the study web site, and in the Help area of the database user interface.

7 References

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8 APPENDICES

8.1 APPENDIX A: Donor schedule of events

Event	Time Point											
	Pre-Donation	At Donation										
	Shortly Pre-Donation	Just Prior to Resection	1° Post Resection	Day 2	Week 1	Month 1	Month 3	Month 6	Year 1	Year 2	Year 3	Year 4
LFTs	**X**				**X**	**X**	**X**		**X**	**X**	**X**	**X**
CBC	**X**				**X**	**X**	**X**		**X**	**X**	**X**	**X**
Creatinine & BUN	**X**				**X**	**X**						
PT/INR	**X**				**X**	**X**	**X**		**X**	**X**	**X**	**X**
CT/MRI	**X**						**X**					
Liver Bx - Biorepository		**X**	**X**									
Whole Blood – DNA Biorepository	**X*** **											
Serum - Biorepository	**X**				**X**	**X**	**X**		**X**			
Plasma & Peripheral Cells - Biorepository	**X**					**X**	**X**		**X**			
Whole Blood - RNA Extraction for future study	**X**					**X**	**X**		**X**			
Post-Donation Pain Survey				X								
Long - term Follow-up Cohort* HRQOL BATTERY (Table 1 in Protocol)										**X**	**X**	**X**
Prospective Cohort** HRQOL BATTERY (Table 2 in Protocol)	**X**						**X**	**X**	**X**	**X**		

* Old donors from new sites will not be getting labs or non-HRQOL-related study visits.
** All new donors from all sites.
***Can be collected at any timepoint during the study.
SUBJECTS JOINING THE STUDY FROM THE PREVIOUS A2ALL COHORT STUDY WHO ARE MORE THAN 4 YEARS POST-TXP WILL FOLLOW AN ANNUAL SCHEDULE OF EVENTS WITH THE SAME ASSESSMENTS AND SAMPLES AS YEAR 4.

8.2 APPENDIX B: Recipient schedule of events

Event	Time Point																									
	Pre-TXP	At TXP						Post TXP																		
	Shortly Pre-TXP	Pre-op	After Portal Dissection	Back Table	After completion of the arterial anastomosis	After portal flow modification*	1° Post Reperfusion	Day 1	Day 2	Day 3	Day 4*	Day 5*	Day 6*	Day 7	Day 8*	Day 9*	Day 10*	Day 11*	Day 12*	Day 13*	Wk 2	Mon 1	Mon 3	Yr 1	Yr 2	Yr 3	Yr 4
LFTs	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/INR	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sodium	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X					
BUN	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X					
HCV RNA																									X ***	
Pressure & Flow Measurements			X		X	X																				
Doppler Portal Vein Flow Rate								X																		
CT/MRI	X																					X				
Liver Bx - Biorepository				X			X																		X ***	
Whole Blood – DNA BioRepository	X**																									
Serum - Biorepository	X													X							X	X	X	X	X	X
Plasma & Peripheral Cells - Biorepository	X																					X	X	X	HCV Plasma Only	
Whole Blood - RNA Extraction for future study	X																					X	X	X	X	

* Record if done clinically
**Can be collected at any time point in the study
***HCV RCP only; Bx performed if no clinical Bx was performed at this timepoint
SUBJECTS JOINING THE STUDY FROM THE PREVIOUS A2ALL COHORT STUDY WHO ARE MORE THAN 4 YEARS POST-TXP WILL FOLLOW AN ANNUAL SCHEDULE OF EVENTS WITH THE SAME ASSESSMENTS AND SAMPLES AS YEAR 4.

8.3 APPENDIX C: Modification WHO grading and management of adverse events

Recommendations for Grading of Adverse Events (Modification of WHO Recommendations)				
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Hematologic (Adults)				
Hemoglobin (g/100 mL)	9.5-10.9	8.0-9.4	6.5-7.9	<6.5
Leukocytes 1000/cmm	2.0-2.9	1.5-1.9	1.0-1.4	<1.0
Neutrophils 1000/cmm	1.0-1.5	0.75-0.99	0.5-0.74	<0.5
Platelets 1000/cmm	70-100	50-69	25-49	<25
Lymphocytes (1000/cmm)	0.5>0.20	0.2>0.10	0.10	
Hemorrhage*	-	mildly symptomatic, no Rx required	gross blood loss or 1-2 units transfused	massive blood loss or >2 units transfused
Gastrointestinal				
Total Bilirubin*	1.26-2.5 x N[§]	2.6-5 x N	5.1-10 x N	Evidence of hepatic failure
AST/ALT (SGOT/SGPT)	2 x Baseline	2.1-5 x Baseline	5.1-10 x Baseline	Evidence of hepatic failure
Alkaline phosphatase	2 x Baseline	2.1-5 x Baseline	5.1-10 x Baseline	Evidence of hepatic failure
Oral/stomatitis	painless ulcers, erythema, or mild soreness	painful erythema, edema or ulcers, but can eat	painful erythema, edema or ulcers, and can not eat	requires parenteral or enteral support
Diarrhea	increase of 2-3 stools/ day of pre-Rx	increase of 4-6 stools/day or nocturnal stools, or moderate cramping	increase of 7-9 stools/day, or incontinence, or severe cramping	increase of 10 stools/day or grossly bloody diarrhea, or need for parenteral support
Constipation	mild	moderate	abdominal distention	distention and vomiting
Renal, Bladder				
BUN or blood urea*	1.26-2.5 x N	2.6-5 x N	5.1-10 x N	>10 x N
Creatinine	>1.5 mg/dL <2.0 mg/dL	2.0 <4.0 mg/dL	4.0 <8.0 mg/dL	>8.0 mg/dL
Proteinuria*	1+, <0.3 g/100 mL	2-3+, 0.3-1.0 g/100 mL	4+, >1.0 g/100 mL	nephrotic syndrome
Hematuria	micro only	gross, no clots	gross + clots	requires transfusion
Pulmonary[¶]	asymptomatic, with abnormality in PFTs	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
Allergic*	transient rash	urticaria, mild bronchospasm	serum sickness, bronchospasm, required parenteral meds	anaphylaxis

Recommendations for Grading of Adverse Events (Modification of WHO Recommendations)				
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Cutaneous/Rash/Dermatitis	erythema, pruritus	diffuse maculopapular rash or dry desquamation	vesiculation or moist desquamation, or ulceration	Any one: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req. surgery, exfoliative dermatitis
Hair*	minimal hair loss	moderate, patchy alopecia	complete alopecia but reversible	nonreversible alopecia
Infection (specify site)*	minor infection	moderate infection	major infection	major infection with hypotension
Cardiac				
Cardiac dysrhythmias	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring or causes hypotension, or ventricular tachycardia, or fibrillation
Function*	asymptomatic, but abnormal cardiac sign	transient symptomatic dysfunction, no therapy required	symptomatic dysfunction responsive to therapy	symptomatic dysfunction nonresponsive to therapy
Cardiac-ischemia	nonspecific T-wave flattening (new ECG changes)	asymptomatic, ST and T-wave changes suggesting ischemia (new ECG changes)	angina without evidence for infarction	acute myocardial infarction
Cardiac-pericardial	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Blood Pressure				
Hypertension	asymptomatic transient increase by greater than 20 mm Hg (0) or to >150/100 if previously WNL; no treatment required	recurrent or persistent increase by greater than 20 mmHg (0) or to >150/100 if previously WNL; no treatment required	requires therapy	hypertensive crisis or hospitalization required for hypertension
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluid Rx	IV fluid req, no hospitalization req.	requires hospitalization
Neurotoxicity*				
Peripheral*	paresthesias and/or decreased tendon reflexes	severe paresthesias and/or mild weakness	intolerable paresthesias and/or marked motor loss	paralysis
Neuromotor (Asthenia)	subjective weakness; no objective findings	mild objective weakness without significant	objective weakness with impairment of function	paralysis, or confined to bed or wheel chair because of

Recommendations for Grading of Adverse Events (Modification of WHO Recommendations)				
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
		impairment of function		muscle weakness
Neurocortical	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, agitation, confusion, disorientation, or hallucinations	coma, seizures, toxic psychosis
Neurocerebellar	slight in coordination or dysdiadochokinesias	intention tremor or dysmetria, or slurred speech, or nystagmus	ataxia requiring assistance to walk or arm incoordination interfering with ADLs	unable to stand
Neuromood	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Neurohearing	asymptomatic hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neurovision	--	--	Symptomatic subtotal loss of vision	blindness
Pain (specify site)	mild	moderate	severe	intractable, requires use of narcotics
Local (specify site)	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated, intractable pain
Flu-like Symptoms				
Fever	up to 38.6 C (101.5 F)	38.7 C-39.9 C (101.7 F-103.8 F)	>40 C (104 F)	Fever with hypotension
Chills	Mild to Moderate Shaking	Severe Shaking	Rigors that incapacitates patient's daily function	--
Headache	<2 hours not requiring analgesic	2 hours, but less than 24 hrs requires analgesic	24 hrs requires multiple doses of analgesic	intractable, requires repeated narcotics
Fatigue	fatigue reported but no effect on daily function	moderate decrease in daily function	fatigue that incapacitates patient's daily function	--
Malaise	<24 hours duration	24-48 hours duration	persistent >48 hours duration	--
Nausea	occasional and transient	persistent >24 hours	persistent >24 hours with daily vomiting	--
Vomiting	sporadic not occurring daily	daily emesis	daily emesis intolerable requiring therapy	intractable vomiting
Weight gain/loss	5.0-9.9%	10.0-19.9%	20.0%	--

Recommendations for Grading of Adverse Events (Modification of WHO Recommendations)				
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Arthralgia	joint pain reported but no effect on daily function	moderate decreases of daily function	joint pain incapacitates patient's daily function	--
Myalgia	muscle pain reported but no effect on daily function	moderate decrease of daily function	muscle pain that incapacitates patient's daily function	--
Thyroid Abnormality[#]				
Hypothyroid	Borderline Elevation TSH (<1.5 N)	Elevated TSH (1.5N), low T_4, no clinical signs or symptoms	Elevated TSH, low T_4 with clinical signs or symptoms requiring thyroid replacement medication	Myxoedema or Myxoedema coma
Hyperthyroid	low TSH	Low TSH, elevated T_4, no clinical signs or symptoms	Low TSH, elevated T_4 with clinical signs or symptoms requiring anti-thyroid medication	thyroid storm, hyperthyroidism poorly or not controlled by antithyroid medication
Metabolic				
Hyperglycemia (mmol/L)	6.4-8.8	8.9-13.7	13.8-27.5	>27.5 or ketoacidosis
Hyperuricemia	ULN 1.5 x N	>1.5 x N, no clinical signs or symptoms	clinical gout	
Hypoglycemia (mmol/L)	3.0-3.5	2.2-2.9	1.7-2.1	<1.7
Amylase	<1.5 X N	1.5-2.0 X N	2.1-5.0 X N	>5.1 X N
Hypercalcemia (mmol/L)	2.6-2.89	2.9-3.09	3.1-3.3	>3.3
Hypocalcemia (mmol/L)	1.9-2.14	1.7-1.89	1.5-1.69	<1.5
Hypomagnesemia (mmol/L)	1.4-1.2	1.1-0.9	0.8-0.6	0.5
Coagulation				
Fibrinogen	0.99-0.75 X N	0.74-0.50 X N	0.49-0.25 X N	0.24 X N
Prothrombin time	1.01-1.25 X N	1.26-1.50 X N	1.51-2.00 X N	>2.00 X N
Partial thromboplastin time	1.01-1.66 X N	1.67-2.33 X N	2.34-3.00 X N	>3.00 X N
Other	reported but no effect on daily function	moderate decrease in daily function	incapacitates patient's daily function	clinical judgment of the investigator with documentation of the clinical criteria used to make the decision

* Miller AB, et. al.: Cancer 47:210-211, 1981 (Items taken from WHO are indicated with an asterisk).

§ N = Upper limit of normal. Therapy should be discontinued for subjects developing thyroid abnormalities during treatment, whose thyroid function can not be normalized by medication.

8.4 APPENDIX D: Potential Subjects for Enrollment into the Core Protocol

Subject Type	Enroll into Core Protocol?	Enroll into HRQOL Sub-study?	HCV Study	Donor Pain Study	Existing Data Sources	Potential Data Entry Methods
Former A2ALL Subjects (continuing centers only)						
Full Cohort Donors Post-donation at the end of Cohort enrollment*	YES	YES	NO	NO	BioDBx***	Upload/New Data Entry
Full Cohort LDLT Recipients Post-transplant at the end of Cohort enrollment*	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Full Cohort DDLT Recipients Post-transplant at the end of Cohort enrollment*	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Cohort Lite Donors Post-donation at the end of Cohort enrollment* (donation occurred from 2002 – 2008)	YES	YES	NO	NO	BioDBx***	Upload/New Data Entry
Cohort Lite LDLT Recipients Post-transplant at the end of Cohort enrollment*	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Cohort Lite DDLT Recipients Post-transplant at the end of Cohort enrollment*	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Donors whose donation occurred in the Gap Era**	YES	NO	NO	NO	BioDBx***	Upload/New Data Entry
LDLT Recipients whose transplant occurred in the Gap Era**(must be three years post-transplant for the HCV Study)	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
DDLT Recipients whose transplant	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry

occurred in the Gap Era**(must be three years post-transplant for the HCV Study)						
New Subjects (all centers)	**Enroll into Core Protocol?**	**Enroll into HRQOL Sub-study?**	**HCV Study**	**Donor Pain Study**	**Existing Data Sources**	**Potential Data Entry Methods**
Actual Donors shortly Pre-donation	YES	YES	NO	YES	NONE	New Data Entry
LDLT Recipients shortly Pre-transplant	YES	NO	NO	NO	NONE	New Data Entry
Donors whose donation occurred in the Gap Era**	YES	NO	NO	NO	NONE	Upload/New Data Entry
LDLT Recipients whose transplant occurred in the Gap Era**(must be three years post-transplant for the HCV Study)	YES	NO	YES	NO	NONE	Upload/New Data Entry
Donors that Donated Prior to the Gap Era** (new centers only)	NO	YES	NO	NO	NONE	Upload/New Data Entry
LDLT Recipients whose transplant occurred during the Cohort Era****	NO	NO	YES	NO	NONE	Upload/New Data Entry
DDLT Recipients with HCV whose transplant occurred during the Cohort Era**** AND had a living donor evaluated(must be three years post-transplant for the HCV Study).	NO	NO	YES	NO	NONE	Upload/New Data Entry

* End of Cohort Enrollment = August 31, 2009
** Gap Era = September 1, 2009 - Site Initiation for Core Protocol (will vary by site)
*** Data for former A2ALL subjects exists in BioDBx up through August 31, 2010. All subjects will be post-transplant/donation. Additional data for the time period September 1, 2010-Site Initiation for Core Protocol will have to be manually entered or uploaded via spreadsheet.
****Cohort Era = March 1, 2003 – Sept. 1, 2010

8.5 APPENDIX E: Retrospective Institutional Pain Management Practice Survey

Introduction

There are a number of ways to treat postoperative pain in live liver donors. However, there is little information available to help physicians choose the best approach. We are conducting a survey to collect information about methods of pain control used for live liver donors and the type of personnel who administer them.

The survey asks about current and past methods used to control pain and your perceptions of their effectiveness. If you do not know the answer to a question, please check "Don't Know" response.

Responses will be reported in aggregate form; individual responses will remain anonymous. You will be asked to indicate the center where you work. This will allow us to determine center-specific practices, but no individual response will be identified.

A. Personnel, Training, and Facility Resources

1. At which transplant center do you work?

- ◯ UCSF
- ◯ University of Colorado
- ◯ Northwestern
- ◯ Toronto
- ◯ University of Pittsburgh
- ◯ University of Pennsylvania
- ◯ VCU
- ◯ Columbia
- ◯ Lahey

2. What is your clinical training?

- ◯ Anesthesiologist
- ◯ Surgeon
- ◯ Nurse
- ◯ Other

Other (please specify)

3. For how many years have you provided acute pain care for live liver donors?

- ◯ <2 years
- ◯ 2-6 years
- ◯ 7-10 years
- ◯ >10 years

4. How many live liver donors did you provide pain care for in the last 12 months?

- ◯ 1-5
- ◯ 6-10
- ◯ 11-15
- ◯ 16-20
- ◯ More that 20

5. Does your hospital have a dedicated Acute Pain Team?

- ◯ Yes
- ◯ No
- ◯ Don't know

6. Are you a member of the Acute Pain Team?

- ◯ Yes
- ◯ No

7. Does the Acute Pain Team provide postoperative pain management to live liver donors?

- ◯ Yes
- ◯ No

8. If the Acute Pain Team does not provide postoperative care, why not? Check all that apply.

- ☐ There is no Acute Pain Team
- ☐ The Acute Pain Team does not have enough expertise with live liver donors
- ☐ The Acute Pain Team is not available enough to provide continuity of care
- ☐ The liver transplant team has not developed a collaboration with the Acute Pain Team
- ☐ Use of the Acute Pain Team takes away control of the patient from the surgical team
- ☐ It is too complicated to have so many care providers
- ☐ Don't Know

9. If there are reasons other than the ones listed above related to why the Acute Pain Team is not used, please specify.

10. What Departments are members of the Acute Pain Team at your institution? Check all that apply.

- ☐ Anesthesiology
- ☐ Surgery
- ☐ Don't Know

Other (please specify)

11. Does the Acute Pain Team provide 24 hour coverage?

- ○ Yes
- ○ No
- ○ Don't know

12. Is there a dedicated team of anesthesiologists that cares for live liver donors in the operating room?

- ○ Yes
- ○ No
- ○ Don't Know

13. Do any of the dedicated live donor intraoperative anesthesiologists serve on the Acute Pain Team?

- ○ Yes
- ○ No
- ○ Don't Know

14. Where are donors admitted for immediate postoperative care?

- ○ ICU (Intensive Care Unit)
- ○ PACU (Post Anesthesia Care Unit)
- ○ Don't Know
- ○ Other, please specify

Other (please specify)

15. What is the average number of days in ICU and/or PACU? Please indicate number for each unit in box, or indicate DNK (do not know)

Care Providers Opinions About Pain Care

This set of questions is about your perceptions pain and pain management for live liver donors. Please indicate how much you agree or disagree with the statements that follow.

21. Our live liver donors receive enough monitoring on the ward for early identification of adverse events.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

22. Pain is assessed frequently enough on the ward.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

23. The severity of pain experienced by live liver donors is greater than other liver resection patients.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

24. The amount of emotional distress experienced by live liver donors due to pain is greater than other liver resection patients.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

16. After ICU/PACU stay is complete, where are donors transferred to?

- ◯ A surgical ward that specializes in transplant care
- ◯ A general surgical ward
- ◯ A step-down unit
- ◯ Don't know

17. Do the nurses on the ward where the live donor is admitted receive formal teaching about postoperative pain management?

- ◯ Yes
- ◯ No
- ◯ Don't know

18. If yes, who provides their formal education?

- ◯ Acute Pain Team
- ◯ Nursing
- ◯ Surgery

Other (please specify)

19. Do live liver donors routinely have continuous monitoring of any vital signs that can be seen at the main nursing desk during their ward stay?

- ◯ Yes
- ◯ No
- ◯ Don't Know

20. If YES, what kind of continuous monitoring is used? Check all that apply.

- ☐ Pulse oximitry
- ☐ EKG
- ☐ Blood pressure
- ☐ Other

Other (please specify)

Care Providers Opinions About Pain Care

This set of questions is about your perceptions pain and pain management for live liver donors. Please indicate how much you agree or disagree with the statements that follow.

21. Our live liver donors receive enough monitoring on the ward for early identification of adverse events.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

22. Pain is assessed frequently enough on the ward.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

23. The severity of pain experienced by live liver donors is greater than other liver resection patients.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

24. The amount of emotional distress experienced by live liver donors due to pain is greater than other liver resection patients.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

25. Health care providers often under treat pain in live liver donors because they are worried about complications of pain medications.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree
- ◯ Don't know

26. Your live liver donors are currently satisfied with their pain management.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

C. Approach to Pain Assessment

The following questions ask about how your institiuion evaluates patients' pain.

27. Indicate all health care providers that routinely perform pain assessment in the ICU.

- [ ] Nursing
- [ ] Acute Pain Team
- [ ] Surgery
- [ ] Attending anesthesiologist
- [ ] ICU physician
- [ ] Don't know

Other (please specify)

28. Indicate all health care providers that routinely perform pain assessment in the PACU.

- [ ] Nursing
- [ ] Acute Pain Team
- [ ] Surgery
- [ ] Attending anesthesiologist
- [ ] ICU physician
- [ ] Don't know

Other (please specify)

29. Please indicate all health care providers that routinely assess pain on the surgical ward.

- [ ] Nursing
- [ ] Acute Pain Team
- [ ] Surgery
- [ ] Attending anesthesiologist
- [ ] Don't know

Other (please specify)

30. What pain related information is routinely recorded? (only data that would be retrievable by chart review)

- ☐ Visual/numerical pain score at rest
- ☐ Visual/numerical pain score with movement
- ☐ Sedation scores
- ☐ Comfort goal
- ☐ Don't know

31. Does your instituion routinely use a standard patient satisfaction survey to assess the efficacy of pain management?

- ◯ Yes
- ◯ No
- ◯ Don't Know

32. If your institution does not use a standard survey to assess satisfaction of live donors with their pain management, how do you assess this information?

Preoperative Preparation, Patient Input and Ongoing Assessment

These questions are about types of interaction that health care providers have with live liver donors prior to surgery. Area of interest include personal interactions and the development and use of protocols for pain management.

33. Does an anesthesiologist see all live liver donors prior to the day of surgery?

- ◯ Yes
- ◯ No
- ◯ Don't Know

34. Does the Acute Pain Team offer to see all live liver donors prior to the day of surgery?

- ◯ Yes
- ◯ No
- ◯ Don't Know

35. Does your institution have a single protocol for pain management in live liver donors?

- ◯ Yes
- ◯ No
- ◯ Don't Know

36. Please check all types of health care providers that participated in the development of this protocol.

- ☐ Anesthesiology
- ☐ Acute Pain Team
- ☐ Surgery
- ☐ Nursing
- ☐ Other, please specify

Other (please specify)

37. If there is no institutional protocol, who decides what pain technique is used? Please check all that apply.

- ☐ Attending Anesthesiologist
- ☐ Surgeon
- ☐ Acute Pain Team
- ☐ Not always the same provider

Other (please specify)

38. Is each live liver donor typically given a choice of pain therapies?

- ◯ Yes
- ◯ No
- ◯ Don't Know

39. Please check all pain management options that are discussed with live liver donors PRIOR TO surgery.

- ☐ Epidural
- ☐ Intrathecal medication
- ☐ Intravenous patient controlled analgesia
- ☐ Oral medication
- ☐ Regional therapy (local infiltration of analgesics/anesthetics)
- ☐ Nonpharmacological (acupuncture, cogmitive behavior etc)
- ☐ Don't Know

Other (please specify)

40. What pain control techniques are currently used at your institution in the immediate postoperative period (48 hours). Please check all that apply.

- ☐ Epidural
- ☐ Intrathecal medication intravenous patient controlled analgesia
- ☐ Oral medication
- ☐ Regional therapy
- ☐ Nonpharmacologic
- ☐ Don't know

Other (please specify)

41. Does a health care provider routinely discuss the amount of postoperative pain that live liver donors should expect to experience prior to surgery?

- ◯ Yes
- ◯ No
- ◯ Don't Know

42. If yes to last question, who discusses pain expectations? Please check all that apply.

- ☐ Anesthesiologist
- ☐ Acute Pain Team
- ☐ Surgeon
- ☐ Nurse
- ☐ Don't know

Other (please specify)

43. Please check all health care providers that make primary decisions about pain management following surgery.

- ☐ Attending anesthesiologist
- ☐ Acute Pain Team
- ☐ Surgery
- ☐ Don't know

Other (please specify)

44. Are there nursing protocols to adjust pain medications for live liver donors without consulting a physician?

- ◯ Yes
- ◯ No
- ◯ Don't Know

45. Who is notified first if the live liver donor does not tolerate the pain?

- ◯ Acute pain team
- ◯ Surgeon
- ◯ Attending anesthesiologist
- ◯ Not always the same provider

Other (please specify)

Details about Pain Techniques

The following questions concern your perceptions of pain management techniques that have been used at you institution.

46. Please check all pain management techniques you currently use in the first 48 hours after surgery. Please provide your opinion regarding each technique listed. If other techniques are used, please list and provide your opinion in the text box that follows the question.

	Epidural	Intrathecal	IVPCA	Local Infiltration
Safe	☐	☐	☐	☐
Works well	☐	☐	☐	☐
Cost Effective	☐	☐	☐	☐
Uses fewer resources	☐	☐	☐	☐
No opinion	☐	☐	☐	☐

Other (please specify)

47. Please check all oral pain medications you currently use in the first 48 hours after donation and provide your opinion regarding the medication. If other agents are utilized, please specify what the agents are and provide your opinion of them.

	Oral Opioid	Gabapentin/Pregabalin	NSAID	Acetaminophen
Safe	☐	☐	☐	☐
Works well	☐	☐	☐	☐
Cost Effective	☐	☐	☐	☐
Uses fewer resources	☐	☐	☐	☐
No opinion	☐	☐	☐	☐

Other (please specify)

48. Has your institution changed pain management techniques since the start of your program?

- ◯ Yes
- ◯ No
- ◯ Don't Know

49. If yes, approximately when was the last time that your program changed techniques?

- ◯ Within the last year
- ◯ From 1 to 2 years ago
- ◯ More than 2 years ago
- ◯ Don't Know

50. If you answered Yes to question 48, how many times has your program changed pain management techniques for live liver donors since the start of your program?

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5 or more

51. Please check all pain control techniques that your center has tried, but does not currently use in the first 48 hours after donation.

- ☐ Epidural
- ☐ Intrathecal
- ☐ IVPCA
- ☐ Local Infiltration

Other (please specify)

52. Please identify the reasons you do not use any of the techniques listed below, even if you have not tried them. If there are other techniques you feel should be included, please list them and add your reasons for not using them.

	Epidural	Intrathecal	IVPCA	Local Infiltration
Patient Complications	☐	☐	☐	☐
Does not work well	☐	☐	☐	☐
Not cost effective	☐	☐	☐	☐
Uses more resources	☐	☐	☐	☐
Personal choice	☐	☐	☐	☐
Don't know	☐	☐	☐	☐
No opinion	☐	☐	☐	☐

Other (please specify)

53. Please check all pain medications your center has tried, but does not currently use in the first 48 hours after donation.

- ◯ Oral Opioid
- ◯ Gabapentin/Pregabalin
- ◯ NSAID
- ◯ Acetaminophen

Other (please specify)

54. Please identify the reasons you do not use the listed medications to control donor pain, even if you have not used them. If there are other agents listed in question 51, please list them in the text box along with reasons for not using them.

	Oral Opioid	Gabapentin/Pregabalin	NSAID	Acetaminophen
Patient Complications	☐	☐	☐	☐
Does not work well	☐	☐	☐	☐
Not cost effective	☐	☐	☐	☐
Uses more resources	☐	☐	☐	☐
Personal choice	☐	☐	☐	☐
Don't know	☐	☐	☐	☐
No opinion	☐	☐	☐	☐

Other (please specify)

55. Please provide any additional comment you would like to make regarding management of live liver donor pain. Thank you for taking the time to complete this survey.

8.6 APPENDIX F: Prospective Living Donor Pain Survey

A2ALL
Adult to Adult Living Donor Liver Transplantation Cohort Study

Donor Pain Study - Patient Information and Assent

Dear Sir / Madam,

We would be grateful if you would participate in our survey on how patients feel after surgery. The aim of the survey is to improve management of pain after live donor surgery.

The information you provide will be made anonymous once you hand in this questionnaire. This means that your name or other form of identification will be deleted from the questionnaire after you hand it in and will not be included in any records we will have.

Your answers in this questionnaire will not be shared with your medical or nursing team.

We can assure you that your team will treat you in the same way whether or not you choose to participate in our survey.

Many thanks for considering to take part in this survey.

Name of Person Administering Survey

Subject ID D

A2ALL Donor Pain Survey

PRINT FORM

Date of First Attempt Time AM PM

Sedation Score

- 0 = Fully Awake
- 1 = Light sedation, largely aware of self/surroundings. Mildly sleepy
- 2 = Moderate sedation, slightly aware of self/surrounds. Somnolent but easily aroused.
- 3 = Deeply sedated, unaware of self/surroundings.
- 4 = General anesthesia, patient is unconscious.

Type of Pain Management (check all that apply)

- Epidural
- Intrathecal
- IVPCA
- Local Infiltration
- Other

Date of Second Attempt Time AM PM Sedation Score

P1. On this scale, please indicate the **least** pain you had in the **FIRST 24 hours**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P1A. On this scale, please indicate the **least** pain you had in the **LAST 24 hours**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P2. On this scale, please indicate the **worst** pain you had in the **LAST 24 hours.**

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P3. What percentage of time in the **LAST 24 hours** were you in **severe pain**?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Never in severe pain										Always in severe pain

Subject ID D

P4. Choose the **one** number below that best describes how much pain **interfered or prevented you from:**

a. Doing **activities in bed** such as turning, sitting up, repositioning:

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
Does not interfere										Completely interferes

b. Doing **activities out of bed** such as walking, sitting in a chair, standing at the sink:

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
Does not interfere										Completely interferes

c. ***Falling*** **asleep:**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
Does not interfere										Completely interferes

d. ***Staying*** **asleep:**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
Does not interfere										Completely interferes

P5. Pain can affect our mood and emotions.
On this scale, please choose the **one** number that best shows how much the pain has caused you to feel:

a. Anxious

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
Not at all										Extremely

b. Depressed

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
Not at all										Extremely

c. Frightened

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○
Not at all										Extremely

Subject ID D

P5. (Cont'd)
On this scale, please choose the **one** number that best shows how much pain caused you to feel:

d. Helpless

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

P6. Have you had any of the following side effects?
Please choose "0" if no; if yes, choose the **one** number that best shows the severity of each:

a. Nausea

0	1	2	3	4	5	6	7	8	9	10
None										Severe

b. Drowsiness

0	1	2	3	4	5	6	7	8	9	10
None										Severe

c. Itching

0	1	2	3	4	5	6	7	8	9	10
None										Severe

d. Dizziness

0	1	2	3	4	5	6	7	8	9	10
None										Severe

P7. In the last 24 hours, how complete has your pain **relief** been?
Please choose the **one** percentage that best shows how much relief you have received from all of your pain treatments combined (medicine and non-medicine treatments).

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

Subject ID D

P8. Were you **allowed to participate in decisions** about your pain treatment as much as you wanted to?

0	1	2	3	4	5	6	7	8	9	10
Not at all										Very much so

P9. Choose the **one** number that best shows how **satisfied** you are with the results of your pain treatment while in the hospital.

0	1	2	3	4	5	6	7	8	9	10
Extremely Dissatisfied										Extremely Satisfied

P10. Did you receive any **information** about your pain treatment options? Yes No

a. If yes, please choose the number that best shows **how helpful** the information was.

0	1	2	3	4	5	6	7	8	9	10
Not at all helpful										Extremely helpful

P11. Did you use any **non-medicine methods** to relieve your pain? Yes No

If yes, **check all** that apply:

- cold pack
- deep breathing
- distraction (such as watching TV, reading)
- heat
- imagery or visualization
- massage
- meditation
- listen to music
- prayer
- relaxation
- walking
- other (specify)

P12. How often did a nurse or doctor **encourage you to use** non-medication methods?

- never
- sometimes
- often

Thank you for your time and feedback!

Study Site	Principal Investigator	Study Coordinator(s)/Contact Information
Columbia-Presbyterian Medical Center New York, New York	Jean E. Emond, MD (Co-Chair of A2ALL Steering Committee)	Tarek Mansour, MB BCH Email: tm2598@columbia.edu Phone: 212-304-5683 Joe Pisa, BA Email: jp3279@columbia.edu Phone: 212-305-3839
Northwestern University Chicago, Illinois	Michael M.I. Abecassis, MD, MBA	Patrice Al-Saden, RN, CCRC Email: palsaden@northwestern.edu Phone: 312-694-0232 Henry Schmidt Email: henry.schmidt@northwestern.org Phone: 312-694-0255 Elizabeth Zerante Email: elizabeth.zerante@northwestern.org Phone: 312-926-0861
University of Pennsylvania Philadelphia, Pennsylvania	Kim M. Olthoff, MD, FACS	Debra McCorriston, RN Email: debra.mccorriston@uphs.upenn.edu Phone: 215-662-2107 Mary Shaw, RN, BBA Email: mary.shaw@uphs.upenn.edu Phone: 215-614-0528
University of Colorado Denver, Aurora, Colorado	James R. Burton, Jr., MD	Jessica Fontenot, BS Email: jessica.fontenot@ucdenver.edu Phone 303-724-1868
University of California, San Francisco San Francisco, California	Chris E. Freise, MD, FACS	Dulce MacLeod, RN Email: dulce.macleod@ucsfmedctr.org Phone: 415-476-3170 (Tu & Th)

Study Site	Principal Investigator	Study Coordinator(s)/Contact Information
Virginia Commonwealth University Richmond, Virginia	Robert A. Fisher, MD, FACS	Joanne Davis, RN Email: jdavis3@mcvh-vcu.edu Phone: 804-828-7921 April Ashworth, RN, BSN Email: aashwort@mcvh-vcu.edu Phone: 804-828-9249 Andrea Lassiter, BS Email: alassiter@mcvh-vcu.edu Phone: 804-828-0485
Lahey Hospital and Medical Center	Elizabeth A. Pomfret, MD, PhD, FACS	Agnes Trabucco, BS, MTASCP Email: agnes.trabucco@lahey.org Phone: 781-744-3367 Nikki Covino, BS Email: nikki.d.covino@lahey.org Phone: 781-744-1454 Erick Marangos Email: erick.marangos@lahey.edu Phone: 781-744-3025
University of Pittsburgh Pittsburgh, Pennsylvania	Abhinav Humar, MD	Sheila Fedorek, RN, CCRC Email: fedoreksp@upmc.edu Phone: 412-682-2207 Leslie Mitrik, BS Email: mitrikla@upmc.edu Phone: 412-682-1645 Megan Basch, RN Email: maschmk@upmc.edu Phone: 412-864-3781
University of Toronto Toronto, Canada	David Grant, MD, FRCSC	Erin Winter, BSc Email: erin.winter@uhn.ca Phone: 416-430-4800 ext: 6093 Kim Castellano, BSc Email: kim.castellano@uhn.ca Phone: 416-340-4800 ext. 5979

DCC Staff	Contact Information
Principal Investigator Robert M. Merion, MD, FACS (Chair of A2ALL Steering Committee)	Email: merionb@umich.edu Phone: 734-369-9395
Co-Investigators Akinololu O. Ojo, MD, PhD Anna S.F. Lok, MD Carl L. Berg, MD Brenda W. Gillespie, PhD	Email: aojo@umich.edu Phone: 734-763-9041 Email: aslok@umich.edu Phone: 734-615-4628 Email: carl.berg@duke.edu Phone: 919-681-4808 Email: bgillesp@umich.edu Phone: 734-647-4609
Project Manager Peg Hill-Callahan, BS, LSW	Email: peg.hill-callahan@arborresearch.org Phone: 734-369-9674
Clinical Monitoring Staff Lead Monitor: Beth Golden, BScN Terese A. Howell, BS, CCRC Lisa A. Holloway, BS, CCRC	Email: beth.golden@arborresearch.org Phone: 734-369-9675 Email: thowell@umich.edu Phone: 734-369-9683 Email: lhollow@umich.edu Phone: 734-369-9682
Project Coordinator Anna Nattie, BA	Email: anna.nattie@arborresearch.org Phone: 734-369-9365
Project Assistant Jenya Abramovich, BA	Email: jenya.abramovich@arborresearch.org Phone: 734-369-9679
Research Staff Managing Analyst: Charlotte A. Beil, MPH Nate Goodrich, MS Abby Smith, MS Sarah Forney, MS Lan Tong, MS	Email: charlotte.beil@arborresearch.org Phone: 734-369-9348 Email: nate.goodrich@arborresearch.org Phone: 734-369-9375 Email: abby.smith@arborresearch.org Phone: 734-369-9681 Email: sarah.forney@arborresearch.org Phone: 734-369-9768 Email: lantong@umich.edu Phone: 734-369-9826

Data and Safety Monitoring Board Charter
Adult to Adult Living Donor Liver Transplant

This charter defines the roles and responsibilities of the Data and Safety Monitoring Board (DSMB) for the Adult to Adult Living Donor Liver Transplant (A2ALL) study group, which is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The DSMB will serve in a consultative capacity to the NIDDK in accordance with the guidelines set forth in this charter. Typically DSMB members review and agree to the charter at the initial meeting. If changes to the charter are necessary, the DSMB reviews and affirms their agreement with the changes. Their concurrence will be noted in the DSMB meeting summary.

DSMB RESPONSIBILITIES

Generally, the first responsibility of the DSMB will be to approve the protocol of the clinical study named above, or the study/studies being undertaken by the research network/consortium named above so that the study can begin enrolling patients. After initial approval, and at periodic intervals during the course of the study, the DSMB responsibilities are to:

- Provide input to assist NIDDK in protecting the safety of the study participants;
- Provide input to the NIDDK on the safety and progress of the study;
- Provide input to the NIDDK on the research protocol, informed consent documents and plans for data safety and monitoring, including all proposed revisions;
- Provide input to the NIDDK on the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the study site, and other factors that may affect study outcome;
- Review areas of concern regarding the performance of individual sites or centers and provide comment to the NIDDK on actions to be considered regarding sites that perform unsatisfactorily;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- Provide input to the NIDDK concerning continuation, termination, or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;
- If appropriate, review the interim analysis of efficacy in accordance with stopping rules which are clearly defined in the protocol and have the approval of the NIDDK with concurrence of the DSMB;
- Provide input to the NIDDK regarding the confidentiality of the study data and the results of monitoring;
- Assist the NIDDK by commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

MEMBERSHIP

The members have been appointed by the NIDDK in consultation with the principal investigator. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the study. Collaborators or associates of the investigators in this study are not eligible to serve on the

DSMB. Written documentation attesting to absence of conflict of interest is required at least annually, and each time there is a change in site investigators and/or institutions involved in the study.

The NIDDK will select a member of the DSMB to serve as the DSMB chairperson. S/He is responsible for overseeing the meetings and developing the agenda in consultation with the NIDDK. The NIDDK will provide the DSMB Executive Secretary. As appropriate, NIDDK personnel may serve as ex-officio (non-voting) members of the DSMB.

DSMB MEETINGS

The DSMB will typically meet twice a year, or as deemed necessary by the NIDDK Program Official with input from the DSMB. An NIDDK representative will be present at every meeting of the DSMB. A quorum of more than half of the DSMB members is required in order to convene a meeting of the DSMB.

Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by the principal investigator and members of his/her staff as well as representatives of the Data Coordinating Center, including the study statistician. Meetings may be convened as conference calls or webinars, as well as in person. In special circumstances, the meetings may also be conducted by email. An emergency meeting of the DSMB may be called at any time by the DSMB chairperson or by the NIDDK Program Official should questions of patient safety arise. The DSMB chairperson must contact the NIDDK Program Official prior to convening any meeting.

MEETING FORMAT

An appropriate format for DSMB meetings consists of an open, closed (if the DSMB is monitoring a study in which the investigators are masked in any way), and executive session. This format may be modified as needed.

Open Session

Members of the DSMB, the NIDDK, the principal investigator and members of the steering committee, including the study biostatistician may attend the open session. Issues discussed will include the conduct and progress of the study, including patient recruitment, data quality, general adherence and toxicity issues, compliance with protocol, and any other logistical matters that may affect either the conduct or outcome of the study. Proposed protocol amendments will also be presented in this session. Patient-specific data and treatment group data may not be presented in the open session.

Closed Session

The closed session will be attended only by DSMB members, unmasked members of the NIDDK, and the unmasked study biostatistician. The discussion at the closed session is completely confidential. All materials from the closed session will be destroyed at the end of the meeting.

Analyses of outcome data are reviewed by masked intervention groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and

examination of any relevant subgroups. The DSMB may request unmasking of the data for either safety or efficacy concerns. Procedures to accomplish unmasking of either individual or treatment group data are to be specified in the Data and Safety Monitoring Plan.

Executive Session
The executive session will be attended by DSMB members and the NIDDK Program Official and the DSMB Executive Secretary. During the executive session, the DSMB will discuss the information presented during the closed and open sessions and provide input on the continuation or termination of the study, protocol modification or other changes to the conduct of the study. The DSMB can be unmasked at any time if trends develop either for benefit or harm to the participants.

The DSMB will make a recommendation for either continuation or termination of the study. Termination may be suggested by the DSMB at any time. Should the DSMB decide to suggest termination of the study, a formal vote of the DSMB will be required. In the event of a split vote, majority vote will rule and the minority opinion will be included in the DSMB meeting summary. Reasons for early termination include:

- Serious adverse effects in entire intervention group or in a dominating subgroup;
- Greater than expected beneficial effects;
- A statistically significant difference by the end of the study is improbable;
- Logistical or data quality problems so severe that correction is not feasible.

Sound rationale for either decision (continuation or termination of the study) should be presented to the NIDDK; this information will not be shared with the investigators until/unless the study is terminated. The NIDDK will make the final decision regarding termination and is responsible for notifying the PI of their (NIDDK's) decision to terminate the study.

REPORTS TO THE DSMB
Interim reports will be prepared by the Data Coordinating Center on a quarterly or semi-annual basis as decided by the NIDDK Program Official and the DSMB. The reports will be distributed to the DSMB, the NIDDK Program Official and the DSMB Executive Secretary at least 10 days prior to a scheduled meeting. These reports shall be provided in sealed envelopes within an express mailing package, by secure email, or by access to a secure website, as the DSMB prefers. The contents of the report are determined by the NIDDK with recommendations from the DSMB. Over time, additions and other modifications to these reports may be directed by the NIDDK and the DSMB on a one-time or continuing basis.

Interim data reports for randomized clinical studies or any study in which the investigators are masked in generally consist of two parts: an Open Report and a Closed Report. For observational studies, generally there will not be a Closed Report.

Open Session Report: This portion of the report provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. This report is generally shared with all investigators involved with the clinical study. The reports contained in this section generally include:

- Comparison of Target Enrollment to Actual Enrollment by Month;
- Comparison of Target Enrollment to Actual Enrollment by Site;

- Overall Subject Status by Site, including: Subjects Screened, Enrolled, Active, Completed and Terminated;
- Demographic and Key Baseline Characteristics by Group;
- Treatment Duration for Subjects who Discontinue Therapy;
- Adverse Events/Serious Adverse Events by Site and Subject.

Closed Session Report: This report may contain data on study outcomes, including safety data, including serious adverse events or termination. Data will be presented by masked treatment groups; however, the DSMB may request that the treatment groups be unmasked to ensure that there are no untoward treatment effects. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting. Data files to be used for interim analyses should have undergone established editing procedures to the extent possible. This report should not be viewed by any members of the clinical study except the designated unmasked study statistician.

DOCUMENTATION OF DSMB MEETINGS

Meeting summary

A formal summary containing the DSMB's input on the conduct of the study and their recommendation regarding continuation of the study will be prepared by the DSMB Executive Secretary. Each DSMB summary will include the DSMB's recommendation regarding continuation or termination of the study. The DSMB meeting summary will not include unmasked data, discussion of the unmasked data, or any other confidential data. Once completed, the summary is sent to the DSMB members for their review and concurrence. When the summary is satisfactory to the DSMB members and concurrence with the summary is received, the summary will be sent to the PI. It is the responsibility of the PI to distribute the summary to all co-investigators.

Substantiation of the DSMB Recommendation Regarding Study Continuation

When requested by the NIDDK, the DSMB will prepare a statement explaining the rationale for their recommendation to continue or terminate the study. This statement will be provided directly to the NIDDK Program Official and will not be shared with the investigators or masked NIDDK personnel.

Letter from the NIDDK Program Official to the Investigators

A letter to the investigators from the NIDDK Program Official will accompany the DSMB summary following each DSMB meeting. This letter will contain any guidance from the NIDDK Program Official in reference to the DSMB summary.

It is the responsibility of the PI to assure that the letter from the Program Official is submitted to all the Institutional Review Boards (IRBs) associated with the study. If the meeting summary is to be submitted to the IRBs in addition to the Program Official's letter, the letter will so state.

CONFIDENTIALITY AND OBJECTIVITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality. Closed

session meeting materials should be destroyed in a secure manner (shredding) following each meeting.

In order to maintain their objectivity, DSMB members are expected not to discuss the study/studies with the investigators except during DSMB meetings. Questions or concerns that arise between DSMB meetings that might lead to discussion between DSMB members and the investigators should be brought to the attention of the NIDDK Program Official.

Adult to Adult Living Donor Liver Transplant (A2ALL)
Data and Safety Monitoring Board Roster

DSMB Members:

J Michael Henderson, MD (Chairperson)
Vice-Chairman, Division of Surgery, E32
Cleveland Clinic
9500 Euclid Ave
Cleveland Ohio 44195-0001
Phone: (216) 444-8462
Fax: (216) 444-8510
Email: Henderm@ccf.org
Assistant: Kathleen Carrick carrick@ccf.org

Ravinder Anand, PhD
Senior Statistician
The EMMES Corporation
Suite 700
401 N. Washington Street
Rockville, MD 20850
Phone: 301-251-1161 x110
Fax: 301-251-1355
Email: ranand@emmes.com

Kimberly A. Brown, MD
Chief, Gastroenterology and Hepatology
Henry Ford Hospital
2799 West Grand Blvd
Detroit, Michigan 48202
Email: kbrown1@hfhs.org
Phone: 313-916-8632
Fax: 313-916-5060
Assistant: Joan Baker
Assistant email:jbaker1@hfhs.org

Roshan Shrestha, MD
Clinical Professor of Medicine
Mercer University School of Medicine
Medical Director of Liver Transplantation
Piedmont Liver Transplant Program
1968 Peachtree Road, NE
77 Building, 6th Floor
Atlanta, GA 30309
Tel: 404-605-2055
Fax: 678-244-6608
Email: Roshan.Shrestha@piedmont.org

NIDDK Representatives

Averell H. Sherker, MD, FRCP(C) (NIDDK Project Scientist for A2ALL)
Scientific Advisor for Viral Hepatitis and Liver Diseases Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Blvd
Room 653, MSC 5450
Bethesda, MD 20892-5450
(for delivery service, use zip code 20817)
Phone: (301) 451-6207
Fax: (301) 480-8300
Email: sherkerah@niddk.nih.gov

Jill P. Smith, MD (NIDDK Program Official for A2ALL)
Director, Clinical & Translational Research in Digestive Diseases
NIDDK
6707 Democracy Blvd, Room 655
Bethesda, MD 20892-5450
Phone: 301-451-2025
Fax: 301-480-8300
Email: jill.smith@nih.gov

Rebecca J. Torrance, RN, MSN (Executive Secretary to the DSMB)
Clinical Trials Specialist
Division of Digestive Diseases and Nutrition
NIDDK
6707 Democracy Blvd
Room 646, MSC 5450
Bethesda, MD 20892-5450
(for delivery service, use zip code 20817)
Phone: (301) 594-7024
Fax: (301) 480-8300
Email: torrancer@niddk.nih.gov

Rebekah Van Raaphorst, MPH (Alternate
Executive Secretary to the DSMB)
Health Research Administrator
Division of Digestive Diseases and Nutrition
NIDDK
6707 Democracy Blvd
Room 648, MSC 5450
Bethesda, MD 20892-5450
(for delivery service, use zip code 20817)
Phone: 301-594-0056
Fax: 301-480-8300
Email: vanraaphr@niddk.nih.gov

Sherry R. Brown, MS
Health Program Analyst
6707 Democracy Blvd, Rm 670A, MSC 5450
Bethesda, MD 20892-5450
(For UPS, FedEx: use 20817)
Phone: (301) 435-8150
Fax: (301) 480-8300
E-mail: browns3@mail.nih.gov

Updated: 7/23/2013

MODEL CONSENT FORM - DONOR

INFORMATION ABOUT THIS DOCUMENT

You may be eligible to take part in a research study – to be a *subject* in an experiment or to let us use information about you to help us learn more about *living donor liver donation.* A primary objective of this study is to learn the long-term effects of donating part of the liver on the donor. This document gives you important information about the study. For example, it describes the purpose, risks, and possible benefits of participating in the study. Please take time to review this document carefully. After you have finished, you should discuss the information here, as well as any questions you have, with the researchers *and your doctor.* If you decide to take part in the study, you will be asked to sign this document. *Do not sign this form unless you understand what the study is about and the risks and possible benefits of participating.*

A2ALL: Adult-to-Adult Living Donor Liver Transplant Study

A. Who is conducting this study?

_____(Physicians names) are conducting a research study that is sponsored by the National Institutes of Health (NIH). Please take time to make your decision and discuss it with your friends and family. Remember that your participation is completely voluntary. A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

B. Why am I invited to participate in this study?

There are several reasons why you may be asked to be a part of this research study.

1. You are being asked to take part in this research study because you have been evaluated as a donor for living donor liver transplantation. After you undergo donor surgery, your doctors plan to study the effect of the surgery on your liver and how the surgery impacts your health and quality of life.

2. You are being asked because you have agreed to serve or have already served as a donor for a living liver donor transplant prior to the start of the current study.

3. Acceptance into this study does not imply acceptance as a living donor by the clinical team.

C. What is the purpose of this study?

A primary objective of this study is looking at the effects on the donor of donating part of the liver. Living donor liver transplantation is a relatively new procedure. The single most important aspect of this procedure is the impact on the donor. There are many important questions that need to be answered regarding the long-term effect of undergoing donor surgery. This study is designed to determine the impact of donor surgery on several specific parts of your health and life. To answer these questions the study will measure:

- Specific details about your surgery.
- Any complications that you might experience immediately after the surgery as well as many months or years later.
- How much pain you experience two days after your donation surgery
- How the surgery impacts the quality of your day-to-day life after the surgery.

Since we need to know how the donation affects you months and years after surgery, we will need to perform tests on you immediately after the surgery and months and years later.

D. Are there Potential Conflicts of Interest?

The investigator of this research does not have any financial interest in the sponsor of this study. The treatments or procedures described in this document are not part of your standard care. You can choose not to participate in the research and still receive standard treatment from your physician.

Because your physician has an interest in this research, you may have questions or concerns about how your decision regarding participation in this research may affect the medical care you receive from your physician. Please feel free to discuss any questions or concerns with your provider. If you wish, you may also request to speak to another provider who is not a member of the research team.

E. How many people will take part in the study?

Approximately 975 liver donor candidates will take part in this NIH sponsored multi-center study, with the participation of nine major liver transplant centers around the United States and Canada.

F. What will I be asked to do?

If you agree to participate in this study and have not yet had your donor operation, we will ask you to undergo testing before the surgery, during the surgery, shortly after the surgery and each year through August 2014. Many of the tests and procedures you will undergo are part of the

normal course of your care. We are also asking you to provide samples of blood, liver tissue, and DNA (genetic material), which will be sent to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repositories (storage facility), a research resource supported by the National Institutes of Health (NIH). The Repository collects, stores, and distributes biological samples and associated data from people with many kinds of disorders, from unaffected family members, and from other healthy people. The purpose of this collection is to make samples available for use in research and teaching for the study of liver disease, after the current study is completed. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases. We will ask you to provide samples to the Repository before, during and one year after your donation surgery.

Since we are interested in how the donation affects your quality of life, you will be contacted by telephone and asked to answer a series of questions. This part of the study will be conducted by our professional survey researchers at the University of Pittsburgh and Northwestern University. We will share your contact information in a secure manner to protect your privacy.

We are also studying donors' perception of how much pain they experience two days after the donation operation and comparing this to how different hospitals manage post-operative pain. On the second day after your operation, a research staff member will come and ask you some questions about how you're feeling. It should take about 15-20 minutes to answer these questions.

If you are joining this study after you had been a living liver donor transplant, it is likely you may have already gone through many of the tests and procedures listed here, because you've already passed these time points in your donation experience. If that's the case, we would like to collect information about you from your existing medical records and ask you to join the study at this point in your care and allow us to perform tests and procedures that are appropriate to your current status and into the future.

We will ask you to do the following <u>before the surgery</u>:

- You will be called on the telephone by our survey researchers to answer questions about your health and well-being as well as your views about the donation process.
- Provide blood cell samples for the NIDDK Biosample Repository. Approximately 12teaspoons or 60 ccs of blood will be collected.
- Undergo an imaging study before your operation (either a Computer Assisted Tomographic (CT) imaging study or a Magnetic Resonance Imaging (MRI) study) to measure the size of your liver and spleen.
- *(insert any other pre-operative tests that are not standard of care at the time points listed in the protocol)*
- The survey questions may take up to 45 minutes to complete.

We will ask you to allow the researchers to perform the following tests on the <u>day of your surgery</u>:

- Provide samples of liver to the NIDDK Biosample Repository.
- Allow the researchers to collect information about your donation surgery
- Allow the researchers to collect information about any complications you develop after your donation.
- *(insert a list of all tests that are not standard of care listed in the protocol for Day 0 at your facility)*

We will ask you to do the following <u>immediately after your surgery</u>:

- Two days after the surgery, we will ask you some questions about your post-operative pain
- Provide blood samples one week after your donation surgery to the NIDDK Biosample Repository. Approximately 5-6teaspoons or 25-30 cc's of blood will be collected
- *(Insert a list of all tests that are not standard of care listed in the protocol during the donation hospitalization).*

We will ask you to do the following <u>throughout the course of the study</u>:

- Provide blood samples to the NIDDK Biosample Repository at week 1, month 1, month 3 and month12. Approximately 10 teaspoons or 50 ccs of blood will be collected at each assessment.
- Return to the transplant center for assessment at month 3, and annually thereafter until August 2014 *(delete timepoints that are standard of care at your facility)*
- Undergo an imaging study at three months after your operation (CT or an MRI) to measure the size of your liver and spleen to see how much your liver has grown back since your donation operation.
- If you entered this study prior to undergoing surgery, answer questions by telephone about your quality of life after donation at 3, 6, 12 and 24 months following donation. These telephone interviews may take up to 45 minutes to complete.
- If you entered the study after living liver donation, answer questions by telephone about your quality of life upon study entry and then annually for three years. These telephone interviews may take up to 45 minutes to complete.
- Allow the researchers to collect information about any complications you develop after your donation operation, until August 2014.
- Allow the researchers to collect information about any hospitalizations that occur after your transplant operation

- *(Insert a list of all tests that are not standard of care listed in the protocol during post-transplant).*

G. How long will I be in the study?

If you agree to participate in this study, you will be asked to undergo testing through August 2014. If you do not donate your liver, your participation in the study will end at the time the

decision is made not to go forward with the operation. We will keep any data/samples collected from you up to that point.

H. Voluntary Withdrawal from Study

Participating in the study is completely **voluntary**. You do not have to participate. You may withdraw from the study at any time. You will not be penalized and will not lose any non-research benefits to which you otherwise may be entitled if you refuse to participate in the study or if you leave the study early. No aspect of your treatment (except the experimental procedures described below) or non-research benefits depends on your enrollment or continued participation in this or any other study.

If you agree to have your sample(s) stored in the Repository, you can change your mind up until the end of the A2ALL study. When study researchers receive written instructions from you, they will destroy your sample and all information that identifies you. After the A2ALL study ends, you will not be able to withdraw your sample because the Repository will not know which one is yours. The sample will stay in the Repository indefinitely. They may be used at any time during that period for more studies about liver donation. You will not be able to find out the results of these tests because your samples will not be able to be traced back to you. Researchers who plan to use your samples for future scientific study will be required to request and receive all of the necessary approvals or waivers from the NIDDK and the A2ALL study investigators before using your sample. Samples will only be released to scientists who are qualified and prepared to conduct a research study.

I. What are the possible risks of the study?

It is important for you to understand that there is a small chance that some research may yield results that may indirectly have a negative impact on insurability, employability, and/or family relationships of some individuals or groups of people.

Sometimes, research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits may be paid back to the researchers and the organizations doing this study. You will not be charged for any of the development costs nor will you receive any financial benefits.

Risks associated with obtaining a blood sample include pain, swelling and bruising at the puncture site.

The main risk of a liver biopsy at the time of your surgery is bleeding. This is usually minimal and your surgeon can treat this at the time of surgery with a small stitch or cautery. Since this is done while you are asleep, the biopsy will not cause discomfort.

Participation in the survey portion of this study involves minimal to no known risks. The only possible risks may be the psychological discomfort some people experience when they discuss personal matters and concerns; or a possible breach of confidentiality. To reduce these potential risks, we are using standardized questionnaires and interviews that are widely used in clinical practice. You may choose not to answer some questions. If you experience psychological distress, we will help you identify an appropriate source for help. In addition, if we learn during the interview that you are having any thoughts about suicide, we will help you identify an appropriate source for help and we will contact your Donor Team to alert them to this need. To minimize possible breaches of confidentiality, your name will not appear on any study forms; only study ID numbers will be used. Your name and your signed consent form will be maintained in a locked file in the Principal Investigator's office. The list linking your name with your ID will be kept in a separate locked file in the Principal Investigator's office.

(Add your institution's boilerplate risk language for every procedure that is performed that is not standard of care at all time points in your facility, i.e. blood draw, liver biopsy, MRI or CT etc.)

J. Are there benefits to taking part in the study?

We cannot promise that you personally will receive any benefits from being in this study. You will not receive any direct benefit or payment for participating (other than a modest payment for completing telephone surveys as outlined below), but your samples may benefit the future health of the community at large or some particular group. Because other researchers will not have access to your identity, neither you nor your physician will get the eventual results of studies that might be performed using your sample.

It is possible that data resulting from use of your samples may eventually be used in a research publication. In that event, your name or other identifying information will not be included, as this information will not be available to the researchers.

K. What other options are there?

If you choose not to participate in this study, you will receive the same medical care and treatment given to all of the other donors.

L. What about confidentiality of my personal information?

All efforts will be made to keep your personal identification confidential. However, it is impossible to guarantee absolute confidentiality. Data from this study will be entered into a computerized database through a secured website. Only authorized personnel with a password will be permitted to enter or view the study data. Except as required by law, as indicated below, your research records will not be released without your prior written consent. If you authorize the release of your records, personnel who are recipients of such records are required by law to maintain their confidentiality.

Organizations that may review your research records include: The National Institutes of Health; Food and Drug Administration (FDA); the Institutional Review Board (IRB), Data Management and Safety Board (DSMB), and the sponsor's representatives (Data Coordinating Center). If the results of the research are published, your name will not be used.

The Repository (central blood sample storage facility) will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. Before the researchers in this study send samples to the Repository, each sample will be given a code number. Your name and all personal identifying information, such as address, social security number, and date of birth, will be removed. Therefore, the Repository will not be able to give out your name, or other information that identifies you to the scientists who receive the samples. However, the Repository and scientists will have some data about you, such as age, sex, diagnosis, {fill in any other data types}, race, and outcomes of the initial study. To help us protect your privacy, The Data Coordinating Center (DCC) will maintain a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. In the event that information regarding intent to harm yourself or others, including child abuse, becomes known to us, we are required by law to divulge this information even without your consent. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Why would my health information be disclosed?

There are many reasons why your health information may be used or disclosed in the course of this study. For example, the researchers may need the information to verify that you are eligible to participate in the study, or to monitor the results, including side effects. Other university and

government officials, safety monitors, and study sponsors may need the information to ensure that the study is conducted properly. Also, information may need to be disclosed to insurance companies or others responsible for your medical bills in order to secure payment.

What information will be disclosed?

If you agree to participate in this study and sign your name on the last page, you will be giving the University Institution (hospitals, health centers, clinics and health care providers) and other providers involved in your care permission to disclose your medical information (doctors' notes, lab results, x-rays, hospital charts, etc.) to the researchers. This includes information relating to: Human Immunodeficiency Virus ("HIV") infection or Acquired Immunodeficiency Syndrome ("AIDS"); treatment for or history of drug or alcohol abuse; and/or mental or behavioral health or psychiatric care.

However, your name and other information that would directly identify you will not be used in any publications or presentations resulting from this research study, unless you give us separate written permission.

How will the researchers protect my privacy?

Your research information will be stored in a locked cabinet and will not be made a part of your regular medical record. However, if the researcher orders any tests, the order and results may become part of your regular medical record. Study data submitted to the DCC will be entered in a secure website that requires a unique name and password and the data will coded to protect your identity. All samples sent to the repository will contain a coded number instead of your name. Any publications that result from this study will not include any identifying information.

The study interviewers at the survey research centers, who will call you to administer the surveys will be given your contact information via a secure, encrypted password-protected file. They will sign a statement indicating that they will abide by confidentiality regulations. Your contact information will be destroyed after the study is over. Data collected during the research will be entered into password-secured databases by research staff authorized by the survey center PIs at Northwestern University (NU) and the University of Pittsburgh (Pitt) to do this.

Other than the research staff, who might see information about me collected during the study, or other related medical records?

- ✓ Institution faculty, staff and contractors responsible for oversight of the research.
- ✓ Government officials who oversee research (such as the federal Office for Human Research Protections and the Food and Drug Administration).
- ✓ Safety monitoring boards that oversee the safety of this study.
- ✓ Research sponsors or funding sources and their representatives.

- ✓ Data Coordinating Center Staff

When does my permission expire? What happens to information about me after the study is over?

Your permission expires at the end of the study. However, even after the study is complete or after you decide to withdraw from the study, information about you may be used or disclosed as follows:

- ✓ To preserve the integrity of the other information collected during the study.
- ✓ As part of a data set used for research, educational and other lawful activities that does not include your name, social security number, or other identifying information.
- ✓ To Institution faculty, staff and agents responsible for oversight of the research.
- ✓ As required by applicable federal or state law. For example, if you withdraw from the study at any time, a record of your withdrawal and the reasons you gave for withdrawing will be kept as part of the study record. In addition, government officials who are responsible for oversight and review of clinical trials may require certain disclosures.

It is important to understand that once your medical records have been disclosed as described above, they may no longer be protected directly by federal privacy regulations issued under the Health Insurance Portability and Accountability Act of 1996 ("HIPAA").

M. What are the costs of my participation in this study?

There is no cost to you or to your insurance company for any of the medical procedures in this study. You will incur costs related to travel back to the transplant center for annual visits as well as missed wages for those days. However, you and your insurance company will be responsible for all costs associated with standard medical care provided to you during your participation in this research. These costs include: surgical expenses, routine clinic visits, procedures, and medications that are part of your standard pre/post donation care.

N. Will I be paid?

You will be offered $20 for completion of each quality of life telephone survey that you complete for this study. *(INSERT if any site compensation e.g. parking, food etc.)*

You should not expect to be reimbursed for lost income due to time away from work.

O. What happens if I need emergency care?

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all safety measures, you might develop medical or psychological complications from participating in this study. In the event of injury or illness resulting from this study, you should contact the *(insert physician's name and number*), the (*Hospital Emergency Room)* at (*Phone #*) or any physician or emergency room. Emergency medical and mental health treatment is available, but will be provided at the usual charge. No funds have been set aside to pay you in the event of injury, however, the (*insert Principal Investigator name*) will provide care for research-related injuries at no charge.

P. What are my rights as a human research participant?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled and will not affect the medical care you receive at (*Hospital Name*).

We will tell you about any new information that may affect your health, welfare, or willingness to continue participation in the study.

Q. Whom do I call if I have questions or problems?

I have been informed that any new information that may affect my willingness to participate in this study will be given to me as it becomes available. If I need to find out more about any aspect of the study, including my rights, I may contact _____ (*Principal Investigator*) or any other attending physician listed on the front page of this consent document. If I have any other questions or concerns about my rights as a research subject, I may contact the Principal Investigator, _____ at _____ (*telephone number*).

If you have any questions or concerns about your rights as a participant in a research study, you may also contact the Medical Institutional Review Board. *(Please include IRB contact information here).*

R. Consent Provisions

Your signature on this form indicates that:

You have had the opportunity to obtain answers to your questions concerning the nature of the experimental study, alternative treatments, if any, and potential discomforts, hazards, side effects and risks related to the research study. You understand that there is a possibility that complications other than those described in this consent form may occur. You realize that although every effort will be made to keep all side effects to a minimum, side effects can be unpredictable both in nature and severity.

You understand that by consenting to participate in the study, you are not waiving any of your legal rights.

You hereby consent to voluntarily take part in the experimental study described above. You understand that you will be fully informed of any changes, which are to be made in this research, before such changes are made, that may affect you as a subject. You further understand that you will be informed of any significant new findings, which develop during the course of this research, which may influence your willingness to continue to participate.

You understand that any information that is obtained in connection with this research and that can be identified with you personally will remain confidential to the extent provided by law. You hereby consent to the release of medical information relating to the experimental study to the National Institutes of Health and the clinical investigators in the study for research purposes. You further consent to the publication in the medical literature of the results of this experimental research, upon the condition that your identity is not disclosed in such medical literature.

One copy of this document will be kept together with the investigators' research records on the study. A second copy will be given to you to keep. A third copy will be placed in your _____ ***(institution name)*** medical record.

(The remainder of this page is left intentionally blank to demonstrate that a portion of the consent text, and the entire signature block, should fit as shown on the following page.)

ACKNOWLEDGED AND AGREED:
SIGNATURE BY THE SUBJECT:

Please sign below if you agree to take part in this study.

- ***You have read the informed consent and/or had it explained to you***
- ***You were given the opportunity to ask questions about the information, and***
- ***You acknowledge your consent to one or both of the following***

☐ ***I acknowledge my consent to provide blood, tissue, cell and information about my donation experience (this information does not contain my name or other identifying information) to the NIDDK Biosample Repository.***

☐ ***I do not agree to provide blood, tissue, cell and information about my donation experience (this information does not contain my name or other identifying information) to the NIDDK Biosample Repository.***

☐ ***I acknowledge my consent to provide blood specimens for DNA extraction and storage at the NIDDK Repository.***

☐ ***I do not agree to provide blood specimens for DNA extraction and storage at the NIDDK Repository.***

_____	_____	_____
Research Subject's Name *(Typed or printed)*	**Research Subject's Signature**	**Date**

OR

_____	_____	_____
Research Subject's Legal Guardian/Representative *(Typed or printed)*	**Legal Guardian's Signature**	**Date**

_____	_____	_____
Witness's Name and title *(Typed or printed)*	**Witness's Signature**	**Date**

(A witness to the research subject's signature is required.)

Signature of person explaining and obtaining the consent:

_____	_____	_____
Name and Title *(Typed or printed)*	**Signature**	**Date**

(NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the research subject. A copy should be placed in the research subject's medical record, if applicable.)

MODEL CONSENT FORM - DONOR (OLD DONORS NEW CENTERS)
***

***Only for use at Pitt, Lahey and Toronto

INFORMATION ABOUT THIS DOCUMENT

You may be eligible to take part in a research study – to be a *subject* in an experiment or to let us use information about you to help us learn more about *living donor liver transplantation*. A primary objective of this study is to learn the long-term effects of donating part of the liver on the donor. This document gives you important information about the study. For example, it describes the purpose, risks, and possible benefits of participating in the study. Please take time to review this document carefully. After you have finished, you should discuss the information here, as well as any questions you have, with the researchers *and your doctor*. If you decide to take part in the study, you will be asked to sign this document. *Do not sign this form unless you understand what the study is about and the risks and possible benefits of participating.*

A2ALL: Adult-to-Adult Living Donor Liver Transplant Study

A. Who is conducting this study?

_____(Physicians names) are conducting a research study that is sponsored by the National Institutes of Health (NIH). Please take time to make your decision and discuss it with your friends and family. Remember that your participation is completely voluntary. A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

B. Why am I invited to participate in this study?

You are being asked because you have already served as a donor for a living liver donor transplant prior to the start of the current study. Your doctors plan to study how the surgery impacts your health and quality of life.

C. What is the purpose of this study?

A primary objective of this study is looking at the effects on the donor of donating part of the liver. Living donor liver transplantation is a relatively new procedure. The single most important aspect of this procedure is the impact on the donor. There are many important questions which need to be answered regarding the long-term effect of undergoing donor surgery. This study is designed to determine the impact of donor surgery on several specific parts of your health and life. To answer these questions the study will measure:

- How the surgery impacts the quality of your day-to-day life after the surgery.

Since we need to know how the donation affects years after surgery, we will need to perform tests on you several years after your operation.

D. Are there Potential Conflicts of Interest?

The investigator of this research does not have any financial interest in the sponsor of this study. The treatments or procedures described in this document are not part of your standard care. You can choose not to participate in the research and still receive standard treatment from your physician.

Because your physician has an interest in this research, you may have questions or concerns about how your decision regarding participation in this research may affect the medical care you receive from your physician. Please feel free to discuss any questions or concerns with your provider. If you wish, you may also request to speak to another provider who is not a member of the research team.

E. How many people will take part in the study?

Approximately 300 liver donor candidates will take part in this NIH sponsored multi-center study, with the participation of nine major liver transplant centers around the United States and Canada.

F. What will I be asked to do?

You will be asked to let us review your medical record and collect information about you, your donation surgery, and if you had any medical problems related to the donation surgery. Since we are interested in how the donation affected your quality of life, you will be contacted by telephone and asked to answer a series of questions. This part of the study will be conducted by our professional survey researchers at the University of Pittsburgh and Northwestern University. We will share your contact information in a secure manner to protect your privacy. You will be asked to answer questions by telephone about your quality of life upon study entry and then annually for three years. These telephone interviews may take up to 45 minutes to complete

G. How long will I be in the study?

If you agree to participate in this study you will be asked to undergo follow-up through August 2014.

H. Voluntary Withdrawal from Study

Participating in the study is completely **voluntary**. You do not have to participate. You may withdraw from the study at any time. You will not be penalized and will not lose any non-research benefits to which you otherwise may be entitled if you refuse to participate in the study or if you leave the study early. No aspect of your treatment (except the experimental procedures described below) or non-research benefits depends on your enrollment or continued participation in this or any other study.

I. What are the possible risks of the study?

It is important for you to understand that there is a small chance that some research may yield results that may indirectly have a negative impact on insurability, employability, and/or family relationships of some individuals or groups of people.

Sometimes, research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits may be paid back to the researchers and the organizations doing this study. You will not be charged for any of the development costs nor will you receive any financial benefits.

Participation in this research study involves minimal to no known risks. The only possible risks may be the psychological discomfort some people experience when they discuss personal matters and concerns; or a possible breach of confidentiality. To reduce these potential risks, we are using standardized questionnaires and interviews that are widely used in clinical practice. You may choose not to answer some questions. If you experience psychological distress, we will help you identify an appropriate source for help. In addition, if we learn during the interview that you are having any thoughts about suicide, we will help you identify an appropriate source for help and we will contact your Donor Team to alert them to this need. To minimize possible breaches of confidentiality, your name will not appear on any study forms; only study ID numbers will be used. Your name and your signed consent form will be maintained in a locked file in the Principal Investigator's office. The list linking your name with your ID will be kept in a separate locked file in the Principal Investigator's office.

J. Are there benefits to taking part in the study?

We cannot promise that you personally will receive any benefits from being in this study.

You will not receive any direct benefit or payment for participating (other than a modest payment for completing telephone surveys as outlined below), but your responses may benefit the future health of the community at large or some particular group. Because other researchers will not have access to your identity, neither you nor your physician will get the eventual results of studies that might be performed using your responses.

It is possible that data resulting from use of your responses may eventually be used in a research publication. In that event, your name or other identifying information will not be included, as this information will not be available to the researchers.

K. What other options are there?

If you choose not to participate in this study, you will receive the same medical care and treatment given to all of the other donors.

L. What about confidentiality of my personal information?

All efforts will be made to keep your personal identification confidential. However, it is impossible to guarantee absolute confidentiality. Data from this study will be entered into a computerized database through a secured website. Only authorized personnel with a password will be permitted to enter or view the study data. Except as required by law, as indicated below, your research records will not be released without your prior written consent. If you authorize the release of your records, personnel who are recipients of such records are required by law to maintain their confidentiality.

Organizations that may review your research records include: The National Institutes of Health; Food and Drug Administration (FDA); the Institutional Review Board (IRB), Data Management and Safety Board (DSMB), and the sponsor's representatives (Data Coordinating Center). If the results of the research are published, your name will not be used.

To help us protect your privacy, The Data Coordinating Center (DCC) will maintain a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. In the event that information regarding intent to harm yourself or others, including child abuse, becomes known to us, we are required by law to divulge this information even without your consent. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Why would my health information be disclosed?

There are many reasons why your health information may be used or disclosed in the course of this study. For example, the researchers may need the information to verify that you are eligible to participate in the study, or to monitor the results, including side effects. Other university and government officials, safety monitors, and study sponsors may need the information to ensure that the study is conducted properly. Also, information may need to be disclosed to insurance companies or others responsible for your medical bills in order to secure payment.

What information will be disclosed?

If you agree to participate in this study and sign your name on the last page, you will be giving the University Institution (hospitals, health centers, clinics and health care providers) and other providers involved in your care permission to disclose your medical information (doctors' notes, lab results, x-rays, hospital charts, etc.) to the researchers. This includes information relating to: Human Immunodeficiency Virus ("HIV") infection or Acquired Immunodeficiency Syndrome ("AIDS"); treatment for or history of drug or alcohol abuse; and/or mental or behavioral health or psychiatric care.

However, your name and other information that would directly identify you will not be used in any publications or presentations resulting from this research study, unless you give us separate written permission.

How will the researchers protect my privacy?

Your research information will be stored in a locked cabinet and will not be made a part of your regular medical record. Study data submitted to the DCC will be entered in a secure website that requires a unique name and password and the data will coded to protect your identity. Any publications that result from this study will not include any identifying information. The study interviewers at the survey research centers, who will call you to administer the surveys will be given your contact information via a secure, encrypted password-protected file. They will sign a statement indicating that they will abide by confidentiality regulations. Your contact information will be destroyed after the study is over. Data collected during the research will be entered into password-secured databases by research staff authorized by the survey center PIs at Northwestern University (NU) and the University of Pittsburgh (Pitt) to do this.

Other than the research staff, who might see information about me collected during the study, or other related medical records?

- ✓ Institution faculty, staff and contractors responsible for oversight of the research.
- ✓ Government officials who oversee research (such as the federal Office for Human Research Protections and the Food and Drug Administration).
- ✓ Safety monitoring boards that oversee the safety of this study.
- ✓ Research sponsors or funding sources and their representatives.
- ✓ Data Coordinating Center Staff

When does my permission expire? What happens to information about me after the study is over?

Your permission expires at the end of the study. However, even after the study is complete or after you decide to withdraw from the study, information about you may be used or disclosed as follows:

- ✓ To preserve the integrity of the other information collected during the study.
- ✓ As part of a data set used for research, educational and other lawful activities that does not include your name, social security number, or other identifying information.
- ✓ To Institution faculty, staff and agents responsible for oversight of the research.
- ✓ As required by applicable federal or state law. For example, if you withdraw from the study at any time, a record of your withdrawal and the reasons you gave for withdrawing will be kept as part of the study record. In addition, government officials who are responsible for oversight and review of clinical trials may require certain disclosures.

It is important to understand that once your medical records have been disclosed as described above, they may no longer be protected directly by federal privacy regulations issued under the Health Insurance Portability and Accountability Act of 1996 ("HIPAA").

M. What are the costs of my participation in this study?

There is no cost to you or to your insurance company for any of the research procedures in this study. However, you and your insurance company will be responsible for all costs associated with standard medical care provided to you during your participation in this research. These costs include: surgical expenses, routine clinic visits, procedures, and medications that are part of your standard post donation care.

N. Will I be paid?

You will be offered $20 for completion of each quality of life telephone survey that you complete for this study. *(INSERT if any site compensation e.g. parking, food etc.)*

You should not expect to be reimbursed for lost income due to time away from work.

O. What happens if I need emergency care?

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all safety measures, you might develop medical or psychological complications from participating in this study. In the event of injury or illness resulting from this study, you should contact the *(insert physician's name and number*), the (*Hospital Emergency Room)* at (*Phone #*) or any physician or emergency room. Emergency medical treatment and mental health care is available, but will be provided at the usual charge. No funds have been set aside to pay you in the event of injury, however, the (*insert Principal Investigator name*) will provide care for research-related injuries at no charge.

P. What are my rights as a human research participant?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled and will not affect the medical care you receive at (*Hospital Name*).

We will tell you about any new information that may affect your health, welfare, or willingness to continue participation in the study.

Q. Whom do I call if I have questions or problems?

I have been informed that any new information that may affect my willingness to participate in this study will be given to me as it becomes available. If I need to find out more about any aspect of the study, including my rights, I may contact _____ (*Principal Investigator*) or any other attending physician listed on the front page of this consent document. If I have any other questions or concerns about my rights as a research subject, I may contact the Principal Investigator, _____ at _____ (*telephone number*).

If you have any questions or concerns about your rights as a participant in a research study you may also contact the Medical Institutional Review Board. *(Please include IRB contact information here).*

R. Consent Provisions

Your signature on this form indicates that:

You have had the opportunity to obtain answers to your questions concerning the nature of the experimental study, alternative treatments, if any, and potential discomforts, hazards, side-effects and risks related to the research study. You understand that there is a possibility that complications other than those described in this consent form may occur. You realize that although every effort will be made to keep all side effects to a minimum, side effects can be unpredictable both in nature and severity.

You understand that by consenting to participate in the study, you are not waiving any of your legal rights.

You hereby consent to voluntarily take part in the experimental study described above. You understand that you will be fully informed of any changes, which are to be made in this research, before such changes are made, that may affect you as a subject. You further understand that you will be informed of any significant new findings, which develop during the course of this research, which may influence your willingness to continue to participate.

You understand that any information that is obtained in connection with this research and that can be identified with you personally will remain confidential to the extent provided by law. You hereby consent to the release of medical information relating to the experimental study to the National Institutes of Health and the clinical investigators in the study for research purposes. You further consent to the publication in the medical literature of the results of this experimental research, upon the condition that your identity is not disclosed in such medical literature.

One copy of this document will be kept together with the investigators' research records on the study. A second copy will be given to you to keep. A third copy will be placed in your _____ ***(institution name)*** medical record.

(The remainder of this page is left intentionally blank to demonstrate that a portion of the consent text, and the entire signature block, should fit as shown on the following page.)

ACKNOWLEDGED AND AGREED:
SIGNATURE BY THE SUBJECT:

Please sign below if you agree to take part in this study.

- ***You have read the informed consent and/or had it explained to you, and***
- ***You were given the opportunity to ask questions about the information***

_____	_____	_____
Research Subject's Name *(Typed or printed)*	**Research Subject's Signature**	**Date**

OR

_____	_____	_____
Research Subject's Legal Guardian/Representative *(Typed or printed)*	**Legal Guardian's Signature**	**Date**

_____	_____	_____
Witness's Name and title *(Typed or printed)*	**Witness's Signature**	**Date**

(A witness to the research subject's signature is required.)

Signature of person explaining and obtaining the consent:

_____	_____	_____
Name and Title *(Typed or printed)*	**Signature**	**Date**

(NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the research subject. A copy should be placed in the research subject's medical record, if applicable.)

MODEL CONSENT FORM - RECIPIENT

INFORMATION ABOUT THIS DOCUMENT

You may be eligible to take part in a research study – to be a *subject* in an experiment or to let us use information about you to help us learn more about living donor liver transplantation. The primary study objective is to analyze outcomes of living liver donation. This document gives you important information about the study. For example, it describes the purpose, risks, and possible benefits of participating in the study. Please take time to review this document carefully. After you have finished, you should discuss the information here, as well as any questions you have, with the researchers *and your doctor.* If you decide to take part in the study, you will be asked to sign this document. *Do not sign this form unless you understand what the study is about and the risks and possible benefits of participating.*

A2ALL: Adult-to-Adult Living Donor Liver Transplant Cohort Study

A. Who is conducting this study?

_____ (Physicians' names) are conducting a research study that is sponsored by the National Institutes of Health (NIH). Please take time to make your decision and discuss it with your friends and family. Remember that your participation is completely voluntary. A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

B. Why am I invited to participate in this study?

There are several reasons why you may be asked to be a part of this research study.

1. You are being asked to take part in this research study because you are currently being evaluated or have previously been evaluated as a recipient of a living donor liver transplant. If you have a living donor liver transplant, your doctors plan to study the effect of the surgery on your liver and how the surgery impacts your health and quality of life. If you were previously evaluated for a living donor transplant but actually received a liver from a deceased donor, your doctors are interested in comparing how you are doing compared to how recipients of living donor livers do.

2. Prior to the start of this study, you received a living donor liver transplant, or were evaluated for a living donor transplant.

C. What is the purpose of this study?

The primary purpose of the study is to analyze the outcomes of living donor liver transplantation. Living donor liver transplantation is a new procedure and there are many important questions, which need to be answered about this surgery. This study is designed to measure the safety and success and determine the impact of surgery on several specific parts of your health and life. To answer these questions the study will measure:

- Specific details about your surgery to determine their impact on your long-term outcome.
- Complications that you might experience immediately after the surgery as well as many months or years later.

Since we need to know how the donation affects you months and years after surgery, we will need to perform tests on you immediately after the surgery and months and years later.

D. Are there Potential Conflicts of Interest?

The investigator of this research does not have any financial interest in the sponsor of this study. The treatments or procedures described in this document are not part of your standard care. You can choose not to participate in the research and still receive standard treatment from your physician.

Because your physician has an interest in this research, you may have questions or concerns about how your decision regarding participation in this research may affect the medical care you receive from your physician. Please feel free to discuss any questions or concerns with your provider. If you wish, you may also request to speak to another provider who is not a member of the research team.

E. How many people will take part in the study?

Approximately 1,070 recipient candidates will take part in this NIH sponsored multi-center study, with the participation of nine major liver transplant centers around the United States and Canada.

F. What will I be asked to do?

If you agree to participate in this study we will ask you to undergo testing before the surgery, immediately after the surgery and each year through August 2014. Many of the tests and procedures you will undergo are part of the normal course of your care. We are also asking you to provide samples of blood, liver tissue, and DNA (genetic material), which will be sent to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repositories (storage facility), a research resource supported by the National Institutes of Health

(NIH). The Repository will store and distribute biological samples and associated data from people with many kinds of disorders, from unaffected family members, and from other healthy people. The purpose of this collection is to make samples available for use in research and teaching for the study of liver disease, after the current study is completed. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases. The samples do not contain any identifying information. They have a code placed on the label to protect your privacy.

If you are joining this study after you had undergone a liver transplant, it is likely you may have already gone through many of the tests and procedures listed here, because you've already passed these time points in your transplant experience. If that's the case, we would like to collect information about you from your medical records and ask you to join the study at this point in your care and allow us to perform tests and procedures that are appropriate to your current status and into the future.

We will ask you to do the following <u>before the surgery</u>:

- Provide blood samples for the NIDDK Biosample Repository. Approximately 12 teaspoons or 60 ccs of blood will be collected.
- Undergo imaging studies (either a Computer Assisted Tomographic (CT) imaging study or a Magnetic Resonance Imaging (MRI) study) to measure the size of your liver and spleen.
- If you have liver cancer or hepatocellular carcinoma (HCC), we will also collect information about your tumor(s) and treatment.

We will ask you to allow the researchers to perform the following tests on the <u>day of your surgery</u>:

- Provide a sample of your new liver to the NIDDK Biosample Repository.
- Provide blood samples immediately before and during your transplant surgery to the NIDDK Biosample Repository.
- Allow the researchers to collect information about your transplant surgery.
- Allow the researchers to collect information about any complications you develop after your transplant.
- During the transplant operation, an ultrasound probe will be applied to the two v essels going to the transplanted liver and we will measure how much blood flows through these vessels to the liver. After less than 5 minutes we will remove the probe. Additionally, we will measure the pressure in one of the vessels, the portal vein, with a very small needle inserted by the surgeon. These measurements will be recorded and analyzed as part of the study.
- During living donor transplant surgery it is occasionally necessary to adjust the blood flow to the liver to improve the function. If your surgeon determines that the flow to the liver needs to be adjusted, the measurements described above will be repeated after the adjustments have been made. These measurements will be recorded and analyzed as part of the study.

- *(insert a list of all tests that are not standard of care listed in the protocol for Day 0 at your facility)*
- If you have HCC, we will collect information about your tumor(s).

We will ask you to do the following immediately after your surgery:

- Provide blood samples during the first and second weeks after your transplant to the NIDDK Biosample Repository.
- Allow the researchers to collect information about your lab results (liver function tests, blood counts, etc.)
- Undergo an ultrasound measurement of the blood flow through your portal vein on the day after your operation
- *(insert a list of all tests that are not standard of care listed in the protocol during the transplant hospitalization)*
- If you have HCC, we will collect information about recurrence and any cancer treatment you receive after your transplant.

We will ask you to do the following throughout the course of the study:

- Provide blood samples to the NIDDK Biosample Repository at months 1, 3, and 12, and annually thereafter through August 2014. Approximately 10teaspoons or 50 ccs of blood will be collected at each assessment.
- Undergo imaging studies at three months after your operation (either a Computer Assisted Tomographic (CT) imaging study or a Magnetic Resonance Imaging (MRI) study) of your liver and spleen to see how much your liver had grown since the transplant operation.
- Return to the transplant center for assessment at months 1, 3, and 12, and annually thereafter through August 2014 *(delete timepoints that are standard of care at your facility)*
- Allow the researchers to collect information about any hospitalizations that occur after your transplant operation
- If you have Hepatitis C (HCV) and are post-transplant, whether you had a liver transplant from a living donor or a deceased donor, we will ask you if we can review your chart and collect information about your pre-transplant HCV treatment, your transplant operation, your immunosuppression medications, rejection episodes, and any HCV treatment you received prior to consenting to this study.
- If you have HCV, we will ask if we can look at your chart for liver biopsy results that occurred at after your transplant.
- If you have not had a liver biopsy at least three years after your transplant, or if you had a liver biopsy at least three years after your transplant but the most recent liver biopsy was more than one year ago, we will ask you to come to the center and get a liver biopsy done.
- If you undergo a study liver biopsy, or we have collected information on a previous biopsy, we will send slides of the liver tissue we obtain to our central pathologist to read. Your name and any other identifying information will not be

on the slide. It will have a code number on it that links back to your clinical data. All of the slides will eventually be stored in the NIDDK Repository.

- If you are unwilling or unable to undergo a liver biopsy, we may ask you to undergo a procedure called "transient elastography". Transient elastography is a non-invasive procedure during which a sound wave is transmitted to your liver through an ultrasound probe, and the time it takes for the sound wave to travel through your liver is measured. Transient elastography is considered to be an experimental procedure. However, it has been well-studied, and there have been no adverse events or injuries associated with its use.
- If you have HCV, we will also collect some blood for storage in the NIDDK Repository. Approximately 10 teaspoons or 50ccs of blood will be collected at this time.
- Allow the researchers to collect information about any complications you develop after your transplant, until August 2014.
- Allow the researchers to collect information about any liver biopsies that are performed after your transplant
- *(insert a list of all tests that are not standard of care listed in the protocol during post-transplant).*

G. How long will I be in the study?

If you agree to participate in this study you will be asked to undergo testing, provide data and samples through August 2014. If you enter the study before you get a transplant and do not receive a liver from a living donor, you will no longer be in the study, and we won't collect any more data or samples from you, although we will keep the data and samples already collected (if any).

H. Voluntary Withdrawal from Study

Participating in the study is completely **voluntary**. You do not have to participate. You may withdraw from the study at any time. You will not be penalized and will not lose any non-research benefits to which you otherwise may be entitled if you refuse to participate in the study or if you leave the study early. No aspect of your treatment (except the experimental procedures described below) or non-research benefits depends on your enrollment or continued participation in this or any other study.

If you agree to have your sample(s) stored in the Repository, you can change your mind up until the end of the A2ALL study. When study researchers receive written instructions from you, they will destroy your sample and all information that identifies you. After the A2ALL study ends, you will not be able to withdraw your sample because the Repository will not know which one is yours. The sample will stay in the Repository indefinitely.

They may be used at any time during that period for more studies about liver disease. You will not be able to find out the results of these tests because your samples will not be able to be traced to back to you. Researchers who plan to use your samples for future scientific study will be required to request and receive all of the necessary approvals or waivers from the NIDDK and A2ALL study investigators before using your samples. Samples will only be released to scientists who are qualified and prepared to conduct a research study.

I. What are the possible risks of the study?

It is important for you to understand that there is a small chance that some research may yield results that may indirectly have a negative impact on insurability, employability, and/or family relationships of some individuals or groups of people.

Sometimes, research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits may be paid back to the researchers and the organizations doing this study. You will not be charged for any of the development costs nor will you receive any financial benefits.

Risks associated with obtaining a blood sample include pain, swelling and bruising at the puncture site.

Risks involved in measuring hepatic artery and portal vein blood flow are minimal, as the probe is placed on top of the vessels for only a short amount of time (less than 5 minutes). There is a small risk of damaging the vessels when placing the probe on top of the vessel. Damage at that point would require repair by your surgeon.

This technique of measuring blood flow is being used at other institutions routinely to ensure adequate blood flow to the new liver after it has been sewn into place. The puncture of the portal vein with a 22 G needle to measure pressures also poses minimal risk: the needle is the smallest available to measure pressure and any hole in the vessel is likely to seal itself off after removal of the needle. However there is a small chance that the vessel may be damaged during the puncture and it would then require a small stitch to repair it. This would be done by your surgeon.

The main risk of a liver biopsy at the time of your surgery is bleeding. This is usually minimal and your surgeon can treat this at the time of surgery with a small stich or cautery. Since this is done while you are asleep, the biopsy will not cause discomfort.

If you have HCV and have not already had a biopsy done at least three years after your transplant operation or if you had a liver biopsy more than three years after your transplant but the most recent one was at least one year ago, we will ask you to undergo one as part of this study. During the biopsy, a needle is put into the liver. A piece of the liver tissue is removed through the needle.

Minor complications such as irritation of the diaphragm muscle by the needle or a small amount of blood could cause pain that is often felt in the right shoulder. This may require an injection of pain medicine. This happens in about 1 out of 5 liver biopsies.

Serious complications occur in roughly 1 in 1,000 people having a biopsy. These include:

- Excessive bleeding from the liver. This may require a blood transfusion and/or an operation to fix.
- The lung may be pierced causing leaking of air from the lung.
- The needle may puncture the bowel or other organs inside the abdomen. They may require further treatment or surgery.

The risk of dying from the procedure is approximately 1 in 10,000 liver biopsies.

If your site's SOC for obtaining a liver Bx is transjugular, please edit this section to reflect the procedure and the associated risks.

(Add your institution's boiler plate risk language for every procedure that is performed that is not standard of care at all time points in your facility, i.e. blood draw,.)

J. Are there benefits to taking part in the study?

We cannot promise that you personally will receive any benefits from being in this study. You will not receive any direct benefit or payment for participating, but your sample may benefit the future health of the community at large or some particular group. Because other researchers will not have access to your identity, neither you nor your physician will get the eventual results of studies that might be performed using your samples.

It is possible that data resulting from use of your sample may eventually be used in a research publication. In that event, your name or other identifying information will not be included, as this information will not be available to the researchers.

K. What other options are there?

If you choose not to participate in this study, you will receive the standard medical care given to liver failure patients.

L. What about confidentiality of my personal information?

All efforts will be made to keep your personal identification confidential. However, it is impossible to guarantee absolute confidentiality. Data from this study will be entered into a computerized database through a secured website. Only authorized personnel with a password will be permitted to enter or view data. Except as required by law, as indicated below, your research records will not be released without your prior written consent. If you authorize the

release of your records, personnel who are recipients of such records are required by law to maintain their confidentiality.

Organizations that may review your research records include: The National Institutes of Health; Food and Drug Administration (FDA); the Institutional Review Board (IRB), Data Management and Safety Board (DSMB), and the sponsor's representatives (Data Coordinating Center). If the results of the research are published, your name will not be used.

The Repository (central blood sample storage facility) will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. Before the researchers in this study send samples to the Repository, each sample will be given a code number. Your name and all personal identifying information, such as address, social security number, and date of birth, will be removed. Therefore, the Repository will not be able to give out your name, or other information that identifies you to the scientists who receive the samples. However, the Repository and scientists will have some data about you, such as age, sex, diagnosis, *{fill in any other data types}*, race, and outcomes of the initial study. To help us protect your privacy, The Data Coordinating Center (DCC) will maintain a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. In the event that information regarding intent to harm yourself or others, including child abuse, becomes known to us, we are required by law to divulge this information even without your consent. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Why would my health information be disclosed?

There are many reasons why your health information may be used or disclosed in the course of this study. For example, the researchers may need the information to verify that you are eligible to participate in the study, or to monitor the results, including side effects. Other university and government officials, safety monitors, and study sponsors may need the information to ensure that the study is conducted properly. Also, information may need to be disclosed to insurance companies or others responsible for your medical bills in order to secure payment.

What information will be disclosed?

If you agree to participate in this study and sign your name on the last page, you will be giving the University/Institution (hospitals, health centers, clinics and health care providers) and other providers involved in your care permission to disclose your medical information (doctors' notes, lab results, x-rays, hospital charts, etc.) to the researchers. This includes information relating to: Human Immunodeficiency Virus ("HIV") infection or Acquired Immunodeficiency Syndrome ("AIDS"); treatment for or history of drug or alcohol abuse; and/or mental or behavioral health or psychiatric care.

However, your name and other information that would directly identify you will not be used in any publications or presentations resulting from this research study, unless you give us separate written permission.

How will the researchers protect my privacy?

Your research information will be stored in a locked cabinet and will not be made a part of your regular medical record. However, if the researcher orders any tests, the order and results may become part of your regular medical record. Study data submitted to the DCC will be entered in a secure website that requires a unique name and password and the data will coded to protect your identity. All samples sent to the repository will contain a coded number instead of your name. Any publications that result from this study will not include any identifying information.

Other than the research staff, who might see information about me collected during the study, or other related medical records?

- ✓ Institution faculty, staff and contractors responsible for oversight of the research.
- ✓ Government officials who oversee research (such as the federal Office for Human Research Protections and the Food and Drug Administration).
- ✓ Safety monitoring boards that oversee the safety of this study.
- ✓ Research sponsors or funding sources and their representatives.
- ✓ Data Coordinating Center Staff

When does my permission expire? What happens to information about me after the study is over?

Your permission expires at the end of the study. However, even after the study is complete or after you decide to withdraw from the study, information about you may be used or disclosed as follows:

- ✓ To preserve the integrity of the other information collected during the study.

- ✓ As part of a data set used for research, educational and other lawful activities that does not include your name, social security number, or other identifying information.
- ✓ To Institution faculty, staff and agents responsible for oversight of the research.
- ✓ As required by applicable federal or state law. For example, if you withdraw from the study at any time, a record of your withdrawal and the reasons you gave for withdrawing will be kept as part of the study record. In addition, government officials who are responsible for oversight and review of clinical trials may require certain disclosures.

It is important to understand that once your medical records have been disclosed as described above, they may no longer be protected directly by federal privacy regulations issued under the Health Insurance Portability and Accountability Act of 1996 ("HIPAA").

M. What are the costs of my participation in this study?

There is no cost to you or to your insurance company for any of the research procedures in this study. However, you and your insurance company will be responsible for all costs associated with standard medical care provided to you during your participation in this research. These costs include: surgical expenses, routine clinic visits, procedures, and medications that are part of your standard pre/post transplant care. What about the liver biopsy? This may not be standard of care in all centers.

N. Will I be paid?

You will not receive any pay for participation in this study. *(INSERT if any site compensation e.g. parking, food etc.)*

You should not expect to be reimbursed for lost income due to time away from work.

O. What happens if I need emergency care?

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all safety measures, you might develop medical complications from participating in this study. In the event of injury or illness resulting from this study, you should contact the *(insert physician's name and number*), the (*Hospital Emergency Room)* at (*Phone #*) or any physician or emergency room. Emergency medical treatment is available, but will be provided at the usual charge. No funds have been set aside to pay you in the event of injury, however, the (*insert Principal Investigator name*) will provide care for research-related injuries at no charge.

P. What are my rights as a human research participant?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled and will not affect the medical care you receive at (*Hospital Name*).

We will tell you about any new information that may affect your health, welfare, or willingness to continue participation in the study.

Q. Whom do I call if I have questions or problems?

I have been informed that any new information that may affect my willingness to participate in this study will be given to me as it becomes available. If I need to find out more about any aspect of the study, including my rights, I may contact _____ (*Principal Investigator*) or any other attending physician listed on the front page of this consent document. If I have any other questions or concerns about my rights as a research subject, I may contact the Principal Investigator, _____ at _____ (*telephone number*).

If you have any questions or concerns about your rights as a participant in a research study you may also contact the Medical Institutional Review Board. *(Please include IRB contact information here).*

R. Consent Provisions

Your signature on this form indicates that:

You have had the opportunity to obtain answers to your questions concerning the nature of the experimental study, alternative treatments, if any, and potential discomforts, hazards, side-effects and risks related to the research study. You understand that there is a possibility that complications other than those described in this consent form may occur. You realize that although every effort will be made to keep all side effects to a minimum, side effects can be unpredictable both in nature and severity.

You understand that by consenting to participate in the study, you are not waiving any of your legal rights.

You hereby consent to voluntarily take part in the experimental study described above. You understand that you will be fully informed of any changes, which are to be made in this research, before such changes are made, that may affect you as a subject. You further understand that you will be informed of any significant new findings, which develop during the course of this research, which may influence your willingness to continue to participate.

You understand that any information that is obtained in connection with this research and that can be identified with you personally will remain confidential to the extent provided by law. You hereby consent to the release of medical information relating to the experimental study to the National Institutes of Health and the clinical investigators in the study for research purposes. You further consent to the publication in the medical literature of the results of this experimental research, upon the condition that your identity is not disclosed in such medical literature.

One copy of this document will be kept together with the investigators' research records on the study. A second copy will be given to you to keep. A third copy will be placed in your _____ ***(institution name)*** medical record.

(The remainder of this page is left intentionally blank to demonstrate that a portion of the consent text, and the entire signature block, should fit as shown on the following page.)

ACKNOWLEDGED AND AGREED:
SIGNATURE BY THE SUBJECT:

Please sign below if you agree to take part in this study.

- ***You have read the informed consent and/or had it explained to you***
- ***You were given the opportunity to ask questions about the information, and***
- ***You acknowledge your consent to one or both of the following***

☐ ***I acknowledge my consent to provide blood, tissue, cell and information about my transplant experience (this information does not contain my name or other identifying information) to the NIDDK Biosample Repository.***

☐ ***I do not agree to provide blood, tissue, cell and information about my transplant experience (this information does not contain my name or other identifying information) to the NIDDK Biosample Repository.***

☐ ***I acknowledge my consent to provide blood specimens for DNA extraction and storage at the NIDDK Repository.***

☐ ***I do not agree to provide blood specimens for DNA extraction and storage at the NIDDK Repository.***

_____	_____	_____
Research Subject's Name *(Typed or printed)*	**Research Subject's Signature**	**Date**

OR

_____	_____	_____
Research Subject's Legal Guardian/Representative *(Typed or printed)*	**Legal Guardian's Signature**	**Date**

_____	_____	_____
Witness's Name and title *(Typed or printed)*	**Witness's Signature**	**Date**

(A witness to the research subject's signature is required.)

Signature of person explaining and obtaining the consent:

_____	_____	_____
Name and Title *(Typed or printed)*	**Signature**	**Date**

(NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the research subject. A copy should be placed in the research subject's medical record, if applicable.)

MODEL CONSENT FORM – HCV RECIPIENT

INFORMATION ABOUT THIS DOCUMENT

You may be eligible to take part in a research study – to be a *subject* in an experiment or to let us use information about you to help us learn more about Hepatitis C (HCV) recurrence after liver transplantation. The primary study objective is to analyze the rate and severity of post-transplant HCV recurrence. This document gives you important information about the study. For example, it describes the purpose, risks, and possible benefits of participating in the study. Please take time to review this document carefully. After you have finished, you should discuss the information here, as well as any questions you have, with the researchers *and your doctor.* If you decide to take part in the study, you will be asked to sign this document. *Do not sign this form unless you understand what the study is about and the risks and possible benefits of participating.*

A2ALL: Adult-to-Adult Living Donor Liver Transplant Cohort Study

A. Who is conducting this study?

_____ (Physicians names) are conducting a research study that is sponsored by the National Institutes of Health (NIH). Please take time to make your decision and discuss it with your friends and family. Remember that your participation is completely voluntary. A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

B. Why am I invited to participate in this study?

- You were diagnosed with Hepatitis C (HCV) prior to receiving a liver transplant.
- Prior to the start of this study, you received a living donor liver transplant, or you were evaluated for a living donor transplant but received a deceased donor transplant.

C. What is the purpose of this study?

The primary purpose of the study is to analyze the rate and severity of post-transplant HCV recurrence between recipients of living donor livers and recipients of livers that came from deceased donors.

D. Are there Potential Conflicts of Interest?

The investigator of this research does not have any financial interest in the sponsor of this study. The treatments or procedures described in this document are not part of your standard care. You can choose not to participate in the research and still receive standard treatment from your physician.

Because your physician has an interest in this research, you may have questions or concerns about how your decision regarding participation in this research may affect the medical care you receive from your physician. Please feel free to discuss any questions or concerns with your provider. If you wish, you may also request to speak to another provider who is not a member of the research team.

E. How many people will take part in the study?

Approximately 500 recipient candidates will take part in this NIH sponsored multi-center study, with the participation of nine major liver transplant centers around the United States and Canada.

F. What will I be asked to do?

We are asking you to provide samples of blood and DNA (genetic material), which will be sent to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repositories (storage facility), a research resource supported by the National Institutes of Health (NIH). The Repository will store and distribute biological samples and associated data from people with many kinds of disorders, from unaffected family members, and from other healthy people. The purpose of this collection is to make samples available for use in research and teaching for the study of liver disease, after the current study is completed. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases. The samples do not contain any identifying information. They have a code placed on the label to protect your privacy.

We would like to collect information about you from your medical records and ask you to join the study at this point in your care and allow us to perform the following tests and procedures:

- We will ask you if we can review your chart and collect information about your pre-transplant HCV treatment, your transplant operation, your immunosuppression medications, rejection episodes, and any HCV treatment you received prior to consenting to this study.
- We will ask if we can look at your chart for liver biopsy results that occurred after your transplant.
- If you have not had a liver biopsy at least three years after your transplant or if you had a liver biopsy at least three years after your transplant but the most recent

liver biopsy was more than one year ago, we will ask you to come to the center and get a liver biopsy done.

- If you undergo a study liver biopsy, or if you had previous biopsies that had not been reviewed centrally, we will send slides of the liver tissue we obtain to our central pathologist to read. Your name and any other identifying information will not be on the slide. It will have a code number on it that links back to your clinical data. After the central pathologist has read the biopsy slides, we will send the slides to be stored in the NIDDK Repository.
- If you are unwilling or unable to undergo a liver biopsy, we may ask you to undergo a procedure called "transient elastography." Transient elastography is a non-invasive procedure during which a sound wave is transmitted to your liver through an ultrasound probe, and the time it takes for the sound wave to travel through your liver is measured. Transient elastography is considered to be an experimental procedure. However, it has been well-studied, and there have been no adverse events or injuries associated with its use.
- We will also collect some blood for storage in the NIDDK Repository. Approximately 10 teaspoons or 50ccs of blood will be collected at this time.

G. How long will I be in the study?

If you agree to participate in this study, you will be asked to undergo testing at one time point only. The duration of your participation may take a few weeks depending on how soon a liver biopsy can be scheduled.

H. Voluntary Withdrawal from Study

Participating in the study is completely **voluntary**. You do not have to participate. You may withdraw from the study at any time. You will not be penalized and will not lose any non-research benefits to which you otherwise may be entitled if you refuse to participate in the study or if you leave the study early. No aspect of your treatment (except the experimental procedures described below) or non-research benefits depends on your enrollment or continued participation in this or any other study.

If you agree to have your sample(s) stored in the Repository, you can change your mind up until the end of the A2ALL study. When study researchers receive written instructions from you, they will destroy your sample and all information that identifies you. After the A2ALL study ends, you will not be able to withdraw your sample because the Repository will not know which one is yours. The sample will stay in the Repository indefinitely.

The samples may be used at any time during that period for more studies about liver disease. You will not be able to find out the results of these tests because your samples will not be able to be traced back to you. Researchers who plan to use your samples for future scientific study will be required to request and receive all of the necessary approvals or waivers from the NIDDK and

A2ALL study investigators before using your samples. Samples will only be released to scientists who are qualified and prepared to conduct a research study.

I. What are the possible risks of the study?

It is important for you to understand that there is a small chance that some research may yield results that may indirectly have a negative impact on insurability, employability, and/or family relationships of some individuals or groups of people.

Sometimes, research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits may be paid back to the researchers and the organizations doing this study. You will not be charged for any of the development costs nor will you receive any financial benefits.

Risks associated with obtaining a blood sample include pain, swelling and bruising at the puncture site.

If you have HCV and have not already had a biopsy done three years after your transplant operation or if you had biopsies more than three years after your transplant but the last one was more than one year ago, we will ask you to undergo a biopsy as part of this study. During the biopsy, a needle is put into the liver. A piece of the liver tissue is removed through the needle.

Minor complications such as irritation of the diaphragm muscle by the needle or a small amount of blood could cause pain that is often felt in the right shoulder. This may require an injection of pain medicine. This happens in about 1 out of 5 liver biopsies.

Serious complications occur in about 1 in 1,000 people having a biopsy. These include:

- Excessive bleeding from the liver. This may require a blood transfusion and/or an operation to fix.
- The lung may be pierced causing leaking of air from the lung.
- The needle may puncture the bowel or other organs inside the abdomen. They may require further treatment or surgery.

The risk of dying from the procedure is approximately 1 in 10,000 liver biopsies.
If transjugular liver Bx is SOC at your site, please add language to this section describing the procedure and detailing the associated risks.

(Add your institution's boiler plate risk language for every procedure that is performed that is not standard of care at all time points in your facility, i.e. blood draw,.)

J. Are there benefits to taking part in the study?

We cannot promise that you personally will receive any benefits from being in this study. You will not receive any direct benefit or payment for participating, but your participation may benefit the future health of the community at large or some particular group. Because other researchers will not have access to your identity, neither you nor your physician will get the eventual results of studies that might be performed using your samples.

It is possible that data resulting from your participation or use of your sample may eventually be used in a research publication. In that event, your name or other identifying information will not be included, as this information will not be available to the researchers.

K. What other options are there?

If you choose not to participate in this study, you will receive the standard medical care given to liver transplant recipients.

L. What about confidentiality of my personal information?

All efforts will be made to keep your personal identification confidential. However, it is impossible to guarantee absolute confidentiality. Data from this study will be entered into a computerized database through a secured website. Only authorized personnel with a password will be permitted to enter or view data. Except as required by law, as indicated below, your research records will not be released without your prior written consent. If you authorize the release of your records, personnel who are recipients of such records are required by law to maintain their confidentiality.

Organizations that may review your research records include: The National Institutes of Health; Food and Drug Administration (FDA); the Institutional Review Board (IRB), Data Management and Safety Board (DSMB), and the sponsor's representatives (Data Coordinating Center). If the results of the research are published, your name will not be used.

The Repository (central blood sample storage facility) will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. Before the researchers in this study send samples to the Repository, each sample will be given a code number. Your name and all personal identifying information, such as address, social security number, and date of birth, will be removed. Therefore, the Repository will not be able to give out your name, or other information that identifies you to the scientists who receive the samples. However, the Repository and scientists will have some data about you, such as age, sex, diagnosis, *{fill in any other data types},* race, and outcomes of the initial study. To help us protect your privacy, The Data Coordinating Center (DCC) will maintain a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the

Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. In the event that information regarding intent to harm yourself or others, including child abuse, becomes known to us, we are required by law to divulge this information even without your consent. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Why would my health information be disclosed?

There are many reasons why your health information may be used or disclosed in the course of this study. For example, the researchers may need the information to verify that you are eligible to participate in the study, or to monitor the results, including side effects. Other university and government officials, safety monitors, and study sponsors may need the information to ensure that the study is conducted properly. Also, information may need to be disclosed to insurance companies or others responsible for your medical bills in order to secure payment.

What information will be disclosed?

If you agree to participate in this study and sign your name on the last page, you will be giving the University/Institution (hospitals, health centers, clinics and health care providers) and other providers involved in your care permission to disclose your medical information (doctors' notes, lab results, x-rays, hospital charts, etc.) to the researchers. This includes information relating to: Human Immunodeficiency Virus ("HIV") infection or Acquired Immunodeficiency Syndrome ("AIDS"); treatment for or history of drug or alcohol abuse; and/or mental or behavioral health or psychiatric care.

However, your name and other information that would directly identify you will not be used in any publications or presentations resulting from this research study, unless you give us separate written permission.

How will the researchers protect my privacy?

Your research information will be stored in a locked cabinet and will not be made a part of your regular medical record. However, if the researcher orders any tests, the order and results may

become part of your regular medical record. Study data submitted to the DCC will be entered in a secure website that requires a unique name and password and the data will coded to protect your identity. All samples sent to the repository will contain a coded number instead of your name. Any publications that result from this study will not include any identifying information.

Other than the research staff, who might see information about me collected during the study, or other related medical records?

- ✓ Institution faculty, staff and contractors responsible for oversight of the research.
- ✓ Government officials who oversee research (such as the federal Office for Human Research Protections and the Food and Drug Administration).
- ✓ Safety monitoring boards that oversee the safety of this study.
- ✓ Research sponsors or funding sources and their representatives.
- ✓ Data Coordinating Center Staff

When does my permission expire? What happens to information about me after the study is over?

Your permission expires at the end of the study. However, even after the study is complete or after you decide to withdraw from the study, information about you may be used or disclosed as follows:

- ✓ To preserve the integrity of the other information collected during the study.
- ✓ As part of a data set used for research, educational and other lawful activities that does not include your name, social security number, or other identifying information.
- ✓ To Institution faculty, staff and agents responsible for oversight of the research.
- ✓ As required by applicable federal or state law. For example, if you withdraw from the study at any time, a record of your withdrawal and the reasons you gave for withdrawing will be kept as part of the study record. In addition, government officials who are responsible for oversight and review of clinical trials may require certain disclosures.

It is important to understand that once your medical records have been disclosed as described above, they may no longer be protected directly by federal privacy regulations issued under the Health Insurance Portability and Accountability Act of 1996 ("HIPAA").

M. What are the costs of my participation in this study?

There is no cost to you or to your insurance company for any of the research procedures in this study. However, you and your insurance company will be responsible for all costs associated with standard medical care provided to you during your participation in this research. These

costs include: surgical expenses, routine clinic visits, procedures, and medications that are part of your standard post transplant care.

N. Will I be paid?

You will not receive any payment for participation in this study. *(INSERT if any site compensation e.g. parking, food etc.)*

You should not expect to be reimbursed for lost income due to time away from work.

O. What happens if I need emergency care?

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all safety measures, you might develop medical complications from participating in this study. In the event of injury or illness resulting from this study, you should contact the *(insert physician's name and number*), the (*Hospital Emergency Room)* at (*Phone #*) or any physician or emergency room. Emergency medical treatment is available, but will be provided at the usual charge. No funds have been set aside to pay you in the event of injury, however, the (*insert Principal Investigator name*) will provide care for research-related injuries at no charge. (insert institutional policy)

P. What are my rights as a human research participant?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled and will not affect the medical care you receive at (*Hospital Name*).

We will tell you about any new information that may affect your health, welfare, or willingness to continue participation in the study.

Q. Whom do I call if I have questions or problems?

I have been informed that any new information that may affect my willingness to participate in this study will be given to me as it becomes available. If I need to find out more about any aspect of the study, including my rights, I may contact _____ (*Principal Investigator*) or any other attending physician listed on the front page of this consent document. If I have any other questions or concerns about my rights as a research subject, I may contact the Principal Investigator, _____ at _____ (*telephone number*).

If you have any questions or concerns about your rights as a participant in a research study you may also contact the Medical Institutional Review Board. *(Please include IRB contact information here).*

R. Consent Provisions

Your signature on this form indicates that:

You have had the opportunity to obtain answers to your questions concerning the nature of the experimental study, alternative treatments, if any, and potential discomforts, hazards, side-effects and risks related to the research study. You understand that there is a possibility that complications other than those described in this consent form may occur. You realize that although every effort will be made to keep all side effects to a minimum, side effects can be unpredictable both in nature and severity.

You understand that by consenting to participate in the study, you are not waiving any of your legal rights.

You hereby consent to voluntarily take part in the experimental study described above. You understand that you will be fully informed of any changes, which are to be made in this research, before such changes are made, that may affect you as a subject. You further understand that you will be informed of any significant new findings, which develop during the course of this research, which may influence your willingness to continue to participate.

You understand that any information that is obtained in connection with this research and that can be identified with you personally will remain confidential to the extent provided by law. You hereby consent to the release of medical information relating to the experimental study to the National Institutes of Health and the clinical investigators in the study for research purposes. You further consent to the publication in the medical literature of the results of this experimental research, upon the condition that your identity is not disclosed in such medical literature.

One copy of this document will be kept together with the investigators' research records on the study. A second copy will be given to you to keep. A third copy will be placed in your _____ ***(institution name)*** medical record.

(The remainder of this page is left intentionally blank to demonstrate that a portion of the consent text, and the entire signature block, should fit as shown on the following page.)

ACKNOWLEDGED AND AGREED:
SIGNATURE BY THE SUBJECT:

Please sign below if you agree to take part in this study.

- ***You have read the informed consent and/or had it explained to you***
- ***You were given the opportunity to ask questions about the information, and***
- ***You acknowledge your consent to one or both of the following***

☐ ***I acknowledge my consent to provide blood, liver tissue and information about my transplant experience (this information does not contain my name or other identifying information) to the NIDDK BiosampleRepository.***

☐ ***I do not agree to provide blood, liver tissue and information about my transplant experience (this information does not contain my name or other identifying information) to the NIDDK Biosample Repository.***

☐ ***I acknowledge my consent to provide blood specimens for DNA extraction and storage at the NIDDK Repository.***

☐ ***I do not agree to provide blood specimens for DNA extraction and storage at the NIDDK Repository.***

_____	_____	_____
Research Subject's Name *(Typed or printed)*	**Research Subject's Signature**	**Date**

OR

_____	_____	_____
Research Subject's Legal <u>Guardian/Representative</u> *(Typed or printed)*	**Legal Guardian's Signature**	**Date**

_____	_____	_____
Witness's Name and title *(Typed or printed)*	**Witness's Signature**	**Date**

(A witness to the research subject's signature is required.)

Signature of person explaining and obtaining the consent:

_____	_____	_____
Name and Title *(Typed or printed)*	**Signature**	**Date**

(NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the research subject. A copy should be placed in the research subject's medical record, if applicable.)

Waiver of Informed Consent

Waiver of project-specific written informed consent is possible if a project meets the following four criteria derived from Section 45 CFR 46.116 (d). "An IRB may … waive the requirements to obtain informed consent, provided the IRB finds and documents that:"

1. The research involves no more than minimal risk to the research subjects. 45 CFR 46.102 (I) defines minimal risk as: "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life of during the performance of routine physical or psychological examinations or tests".

2. The waiver or alteration will not adversely affect the rights and welfare of the research subjects.

3. The research could not practicably be carried out without the waiver or alteration; and;

4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The proposed A2ALL-2 studies meet the above four criteria necessary for consideration of a waiver of consent.

1. The research will abstract information from the following subject populations:
    a. Liver transplant recipients with a hepatitis C virus (HCV) diagnosis who are now deceased, had a graft failure, or who did not undergo the study biopsy.
    b. Transplant recipients and living donors who reached a study endpoint (death, re-transplant, graft failure or transplant (donors) during the "Gap Period".
    c. Deceased liver donors who donated to HCV recipients.
    - The information will be collected from standard medical records from routine medical evaluations and follow-up.
    - The risk to the living subjects of this data abstraction is judged to be minimal. Safeguards are in place to keep the information confidential utilizing a secure server for web-based data entry.
    - The data will be stored on a secure server within the Arbor Research Collaborative for Health computer system.

2. A waiver of written informed consent will not adversely affect the rights or welfare of the living research subjects. These data will consist of clinical and routine laboratory information, donation or transplantation history, hospitalizations, complications, HCV treatment history, liver histology and overall level of health that have been recorded in the subject's medical record.

3. The inclusion of every liver transplant recipient diagnosed with HCV who reached an endpoint or did not undergo the study biopsy is critical to the study's analysis. There are well-documented investigations of the bias introduced by the informed consent process and survivor bias. In order to avoid these biases and examine the overall effect of HCV disease progression, every transplant recipient diagnosed with HCV must be examined. Contacting and securing informed consent from each of those living subjects who do not enroll is "impracticable".

   The inclusion of transplant recipients and living donors who died, were retransplanted or received a liver transplant following living liver donation during the "Gap Period" is critical to the study's analysis in order to avoid a survival bias. Contacting and securing informed consent from each of those living subjects who do not enroll is "impracticable".

   The inclusion of deceased liver donors who donated to HCV recipients is necessary to provide additional data when comparing the long-term outcomes in recipients of LDLT and DDLT with recurrent HCV infection. A waiver of consent is the only way researchers can collect data on deceased patients for the study.

   The inclusion of recipients, who are not registered in the A2ALL-2 Core Protocol (based on ineligibility, dead, or lost to follow-up), but their donors are consented and enrolled in the Core Protocol is necessary. In order to correlate donor Quality of Life (QOL) with recipient outcomes, it is necessary to know about all recipient outcomes, otherwise we would have a biased sample. This requires review of the recipient's medical record though waiver of consent.

4. Information that is revealed from this study will be presented at transplant meetings and published in scientific periodicals. The National Institutes of Health (NIH) will also utilize press releases to communicate the study findings.

We assert that this study will meet the federal regulation requirements for a waiver of informed consent. We appreciate your careful consideration of this request and encourage you to contact us if you have any questions.

Additionally, this study is also eligible for a waiver of consent under the HIPAA guidelines.

The HIPAA requirements for a waiver of consent are:

Waiver criteria:164.512(i)(2)(ii)

1. The research involves no more than minimal risk.
   The research study is limited to accessing, collecting and analyzing existing medical record information. There are no physical or psychological risks to the subjects associated with the conduct of this research.
2. The use or disclosure of the PHI involves no more than the minimal risk to the privacy of the subjects.

Secure web servers and limited access to the data will protect the data from improper use/disclosure.

3. The research cannot practically be conducted without the waiver or alteration.
   It is not possible to conduct this research study without access to and the use of protected health information. The patients, who protected health information will be accessed under this waiver request, have not previously provided informed consent for this research activity. Thus, obtaining the HIPAA authorization of these patients for the research use of their health information is impractical.
4. The waiver will not adversely affect the rights and welfare of the subjects.
   Consistent with this waiver request, access to and the recording and use of identifiable medical record information for the purpose of this research study will be limited to investigators and research staff involved in the conduct of the study. The investigators would have knowledge of and access to such identifiable medical record information for the patient, granting of this waiver will not adversely affect the privacy of the involved patients or the confidentiality of their medical record information.
5. The research could not practically be conducted without access to and use of the protected health information (PHI).
   Access to and the collection and analysis of protected health information is necessary in order to conduct this research study. Consistent with the "minimum necessary standard" of the HIPAA privacy rule, we will only access and collect the specific health information necessary to complete this research study. The Data Coordinating Center (DCC) will maintain the database which contains the data elements obtained from the medical record review. At all times, the data will be stored and transferred via secure data servers that require username and password access. PHI is only visible at the sites and is encrypted. PHI is not visible to the DCC. The DCC will provide a written assurance that the information will be not reused or disclosed.

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This application to the IRBMED is to present the A2ALL-2 Core Protocol for review.

NIDDK INFORMATION SHEET TO DATA COORDINATING CENTERS AND CLINICAL SITES REGARDING NEW FDA REQUIREMENT FOR INFORMED CONSENT DOCUMENTS

WHAT IS THE PURPOSE OF THIS INFORMATION SHEET?

The purpose of this document is to provide information to the NIDDK Data Coordinating Centers (DCCs) and clinical sites regarding the new required informed consent element.

The Food and Drug Administration (FDA) has amended the informed consent regulations in accordance with the Food and Drug Administration Amendments Act of 2007 (FDAAA). Informed consent documents and processes for applicable drug and device trials will be required to include a specific statement to inform potential clinical trial participants that clinical trial information for "applicable trials" has been or will be entered into the NIH clinical trial registry databank that is publicly assessable via ClinicalTrials.gov.

The submission of information of applicable clinical trials to the ClinicalTrial.gov data bank is required by law and is designed to promote transparency of clinical research to study participants and patients.

The FDA expects that the inclusion of such a statement will assure the participant that their participation in the trial contributes to the advancement of medical knowledge. The transparency of this information to the study subject is in keeping with the current basic element of informed consent to inform the participant of a "description of any benefits to the subjects or to others which may reasonably be expected from the research."

HOW DOES THIS AFFECT THE DATA COORDINATING CENTERS AND CLINICAL SITES?

DCCs and clinical sites should ensure that their informed consent templates are in compliance with the new required statement for applicable clinical trials as a "Basic Element of Informed Consent" as described in 21 CFR 50.25(a), not an "Additional Element" per 21 CFR 50.25(b). In addition, investigators and site personnel should be fully trained and capable of accurately describing the ClinicalTrials.gov data bank in discussions with potential human study subjects.

Please refer to the Question & Answer section of this document for more information.

WHAT IS CONSIDERED AN APPLICABLE CLINICAL TRIAL?

This new requirement will affect all clinical investigations that are considered "applicable clinical trials" subject to registration with ClinicalTrials.gov.

A clinical investigation that meets all four of the operative terms is considered an "applicable clinical trial." Conversely, a clinical investigation that does not meet one or more of these criteria would not be considered an applicable drug clinical trial.

Trials of Drugs and Biologics: 1) Controlled, 2) clinical investigation, 3) other than a Phase I investigation, 4) of a drug or biologic product subject to IND regulations or is exempt from IND regulations.

Trials of Devices: 1) Controlled clinical trial with health outcomes; 2) to compare an intervention with a device against a control in human subjects; 3) of a product subject to IDE regulation; 4) and is other than a small feasibility study.

WHAT IS THE SPECIFIC REQUIRED LANGUAGE?

"A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

WHAT IS THE TIMELINE FOR COMPLIANCE?

The compliance date for the new statutory requirement is March 7, 2012. Therefore, all informed consent documents and processes related to an applicable clinical investigation that are initiated ON or AFTER March 7, 2012 must include this new required language.

QUESTIONS & ANSWERS:

Question: Is the new required element consistent between the regulations governing applicable clinical trials of FDA-regulated products (21 CFR 50) and regulations governing clinical trials funded or supported by HHS (45 CFR 46)?

Answer: *Yes. The new required informed consent element does not conflict with any existing regulations for federally funded clinical studies.*

Question: The compliance date refers to clinical investigations initiated on or after March 7, 2012. What is the definition of "initiation"?

Answer: *A clinical trial has been initiated if the sponsor/investigator has had any informed consent documents for that clinical investigation cleared or approved by an IRB, a regulatory body, or other human subjects review entity.*

Question: If the study is a multi-center trial with several IRBs approving the informed consent documents in a staggered fashion, when is the trial considered initiated?

Answer: *If the study is a multi-center study and informed consent documents have been cleared or approved for one or more sites before the compliance date, but not for all sites, the clinical investigation will be considered to have initiated before the compliance date. The informed consent documents for the remaining clinical investigation sites would be considered part of the clinical investigation that initiated prior to the compliance date.*

Question: Is it required to re-consent subjects based solely on the new informed consent requirement for trials that have been initiated before the compliance date?

Answer: *No. Re-consent is not required for trials initiated before the compliance date.*

Question: If a trial is ongoing at the time of the compliance date and is amended for any other purpose, will the new informed consent requirement be applicable?

Answer: *No. Compliance with the new informed consent requirement would not be required. If subjects need to be re-consented, it would only need to include information relating to the purpose of the amendment. However, inclusion of the new informed consent statement in this circumstance is not prohibited.*

Question: Can the new informed consent language be modified by the sponsor or at each clinical site?

Answer: *No. The language must not be modified in order to ensure consistency and ease of review by the IRBs or other review entities. The FDA wants to ensure that potential clinical trial participants receive a consistent and accurate message and are directed to the specific website that contains the clinical trial databank. However, sponsors and investigators are allowed to provide additional explanation/information in the informed consent or other supporting documents.*

Question: Is there a specific section of the informed consent form where the new element should be placed?

Answer: *There is no requirement for the new statement to be located in any particular section of the consent form. The investigators, sponsors, and IRBs have the flexibility to place the new statement in the consent form where they believe it best serves the subjects' interest.*

Question: Is it mandatory that the language for the new element be included in the main informed consent form or can this language be provided to the subjects in a separate information sheet where ClinicalTrials.gov can be explained in simple terms?

Answer: *FDAAA requires that the new element be included in the informed consent documents and processes, not in an information sheet separate from the informed consent documents. However, a clinical site may also provide additional information in a separate sheet.*

Question: Is this requirement also for applicable clinical trials outside of the U.S.?

Answer: *Yes. This requirement is for all trials under FDA jurisdiction (i.e., under IND/IDE) that are registered with the clinical trial databank regardless of location of clinical sites.*

Question: De-identified data is exempt from human subject regulation. Does the required new informed consent statement apply to the de-identified data entered in the clinical trial registry?

Answer: *Yes, the new informed consent statement does apply to the de-identified data that will be entered in the clinical trial registry.*

Question: What if my clinical trial does not meet the definition of an "applicable clinical trial" but is required by the journal to register with clinicaltrials.gov? Do I have to include the new element in my informed consent?

Answer: *The regulations are specifically regarding "applicable clinical trials". Therefore, if a trial does not meet that definition, it is not required per the regulations to include the new element/statement in its informed consent. However, inclusion of this statement is voluntary and can be informative to subjects regardless of whether a trial is an "applicable clinical trial".*

Questions: Where can I find more information on the new requirements for informed consent?

Answer: *Additional information can be found in the Federal Register located at the following link http://edocket.access.gpo.gov/2011/2010-33193.htm*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Institute of Diabetes and
Digestive and Kidney Diseases
Bethesda, Maryland 20892

October 16, 2012

Robert Merion, MD
Professor of Surgery
University of Michigan Health System
2926 Taubman Center, SPC5300
1500 East Medical Center Drive
Ann Arbor, MI 48109

Re: Amendment to Certificate of Confidentiality: DK-04-009 #1

Dear Dr. Merion:

This letter amends the Confidentiality Certificate protecting the identity of research subjects in your project entitled, "A2ALL: Adult-to-Adult Living Donor Liver Transplant Cohort Study."

Specifically, this amendment modifies the existing Certificate by adding/modifying the following aims:

Primary Aim 2: To characterize the differences between LDLT and DDLT in terms of recipient post-transplant outcomes including patient and graft survival, surgical morbidity and resource utilization.

1. To continue to discern the long –term risks and benefits associated with choosing a living donor vs. deceased donor liver transplant with respect to the following metrics:
    - Patient and graft survival analysis starting from time of transplantation
    - Comparison of the incidence of defined medical and surgical complications after transplant between LDLT and DDLT
    - Comparison of resource utilization (hospitalization) between LDLT and DDLT.

Primary Aim 5: To compare the long-term histological outcomes in recipients of LDLT and DDLT with recurrent HCV infection.

1. To determine whether recurrent hepatitis C in LDLT recipient is associated with less severe histological fibrosis (particularly, slower rate of progression to cirrhosis) compared to DLT recipients.

Primary Aim 6: To understand the history of pain management and to measure quality of care in pain control in living donors following partial hepatectomy.

1. To understand each institution's previous experience with pain management in living donors utilizing a retrospective survey of appropriate medical staff to:
    - Determine all methods and personnel at each center used to manage postoperative pain in the liver donors since the start of the program
    - Identify how pain was assessed during the postoperative period (current and previous assessment methods)
    - Identify methods care providers used to assess the outcome (quality) if pain management
2. To measure the quality of postoperative pain management in live liver donor and identify areas of improvement. After implementing a single method (patient survey) instrument for reporting quality indicators at all nine A2ALL centers, the investigators will:
    - Assess overall patient satisfaction with pain management
    - Assess satisfaction with aspects of pain management thought to affect overall patient satisfaction
    - Identify quality indicators that differ in overall donor satisfaction.

Reasons for Requesting a Certificate:

We wish to protect the identities of our subjects as much as possible. In addition to collecting PHI at the site level (display of this information is encrypted and only visible at the site); we will also be collecting sensitive information regarding HIV and hepatitis status and information about voluntary partial live liver donation. Also, many of the clinical site's IRBs require that the study have e Certificate of Confidentiality.

Please note that the Certificate of Confidentiality, DK-04-009 expires on August 31, 2014.

Please attach this amendment to the original Certificate.

If you determine that the research project will not be completed by the expiration date, it will be necessary to submit a written request for an extension of the Certificate **three months prior to the expiration date**. Any such request must include the justification for the extension, documentation of the most recent IRB approval, and the expected date for completion of the research project. In addition, IRB approval must be maintained throughout the length of the study. Approval must be current and unconditional, or conditioned only upon the issuance of a Certificate of Confidentiality and documented by a letter or form signed by an authorized IRB representative

Correspondence should be sent to:

Francisco O. Calvo, Ph.D.
Chief, Review Branch
6707 Democracy Boulevard, Room 752
Bethesda, MD 20892-5452
Phone: (301) 594-8897
Fax: (301) 480-4126

Sincerely,

Gregory G. Germino, MD
Deputy Director
National Institute of Diabetes and
Digestive and Kidney Diseases
National Institutes of Health

Cc: James A. Ashton-Miller, PhD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Institute of Diabetes and
Digestive and Kidney Diseases
Bethesda, Maryland 20892

January 12, 2011

Robert M. Merion, MD
Professor of Surgery
University of Michigan Health system
2926 Taubman Center, SPC5300
1500 East Medical Center Drive
Ann Arbor, MI 48109

Dear Dr. Merion:

Enclosed is the Certificate of Confidentiality, DK-04-009 Certificate extension #2, protecting the identity of research subjects in your project entitled, "A2ALL: Adult to Adult Living Donor Liver Transplant Cohort Study." Please note that the Certificate expires on August 31, 2014.

Please be sure that the consent form given to research participants accurately states the intended uses of personally identifiable information (including matters subject to reporting) and the confidentiality protections, including the protection provided by the Certificate of Confidentiality with its limits and exceptions.

If you determine that the research project will not be completed by the expiration date, August 31, 2014, you must submit a written request for an extension of the Certificate **three months** prior to the expiration date. If you make any changes to the protocol for this study, you should contact me regarding modification of this Certificate. Any requests for modifications of this Certificate must include the reason for the request, documentation of the most recent IRB approval, and the expected date for completion of the research project.

Please advise me of any situation in which the Certificate is employed to resist disclosure of information in legal proceedings. Should attorneys for the project wish to discuss the use of the certificate, they may contact the Office of the NIH Legal Advisor, National Institutes of Health, at (301) 496-6043.

Correspondence should be sent to:

Francisco O. Calvo, Ph.D.
Chief, Review Branch
National Institute of Diabetes and
Digestive and Kidney Diseases
National Institutes of Health
6707 Democracy Blvd, Room 752
Bethesda, MD 20892-5452

Sincerely,

Francisco O. Calvo

Francisco O. Calvo, Ph.D.
Certificate Coordinator

Cc. Ms. Judy A. Nowak

CONFIDENTIALITY CERTIFICATE

DK-04-009

Issued to

University of Michigan Health System

conducting research known as

A2All: Adult-to-Adult Living Donor Liver Transplant Cohort Study

In accordance with the provisions of section 301(d) of the Public Health Service Act 42 U.S.C. 241(d), this Certificate is issued in response to the request of the Principal Investigator, Robert M. Merion, M.D., to protect the privacy of research subjects by withholding their identities from all persons not connected with this research. Dr. Merion is primarily responsible for the conduct of this research, which is supported by the Institute of Diabetes and Digestive and Kidney Diseases.

Under the authority vested in the Secretary of Health and Human Services by section 301(d), all persons who:

1. are enrolled in, employed by, or associated with the University of Michigan Health System and its contractors or cooperating agencies, (e.g., the participating sites) and

2. have in the course of their employment or association access to information that would identify individuals who are the subjects of the research pertaining to the project known as "A2ALL: Adult-to-Adult Living Donor Liver Transplant Cohort Study",

are hereby authorized to protect the privacy of the individuals who are the subjects of that research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research.

There are four primary aims of this project: 1. To quantify the impact of choosing living donor liver transplant (LDLT) on the candidate for transplantation; 2. to characterize the differences between LDLT and DDLT in terms of post-transplant outcomes including patient and graft survival, surgical morbidity, and resource utilization on the recipient of a transplant; 3. to determine the short and long term health and quality of life (QOL) impact of donation, including (a) morbidity after liver donation, and (b) long term health-related QOL of donors compared to control population; and , 4. to standardize and assess the role of "informed consent" in affecting the decision to donate and satisfaction after living liver donation.

An estimated 1,070 potential recipients for liver transplantation will be evaluated and invited to participate from nine clinical centers. Approximately 1,400 potential donors will be enrolled at the time of initial screening history and physical examination, and will either go on to donate, or

may serve as a control population for assessment of the impact of donation on the donors. The age, gender and race distribution is expected to vary similarly to the transplant population. There are no exclusions based on age, race or gender. Blood will be collected and sent to the NIDDK Genetics Repository and to the biosample repository. Liver tissue will be collected and submitted to the biosample repository. Data will be abstracted from the subject's medical record and electronically captured via a secure web interface.

A Certificate of Confidentiality is needed because sensitive information about HIV and Hepatitis status, as well as information about live liver donation will be collected during the course of the study. The Certificate will help researchers avoid involuntary disclosure that could expose subjects or their families to adverse economic, legal, psychological and social consequences.

All blood, tissue and data will be coded with unique study numbers and will not contain identifiable information. Linking information is kept in locked files at the individual sites. Identifiers will be destroyed when the study and data analyses have been completed. Secure web-based data capture system is accessible to study personnel only and protected by user name and password.

This research is underway and is expected to end on July 31, 2009.

As provided in section 301 (d) of the Public Health Service Act 42 U.S.C. 241(d):

> "Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

This Certificate does not protect you from being compelled to make disclosures that: (1) have been consented to in writing by the research subject or the subject's legally authorized representative; (2) are required by the Federal Food, Drug, and Cosmetic Act (21. U.S.C. 301 et seq.) or regulations issued under that Act; or (3) have been requested from a research project funded by NIH or DHHS by authorized representatives of those agencies for the purpose of audit or program review.

This Certificate does not represent an endorsement of the research project by the Department of Health and Human Services. This Certificate is now in effect and will expire on July 31, 2009. The protection afforded by this Confidentiality Certificate is permanent with respect to subjects who participate in the research during the time the Certificate is in effect.

Date: 8/16/04

Joyce A. Hunter

Joyce A. Hunter, Ph.D.
Deputy Director, Division of Extramural Activities
National Institute of Diabetes and Digestive and Kidney Diseases

Organizing your Regulatory Binder

The following is a list of required regulatory items for the A2ALL Core Study Protocol. Refer to the Manual of Operations (MOO) for specifics on each document. For ease in reviewing, assemble your regulatory binder in this way:

1. Study Protocol
2. Investigators and Co-investigators CV's and medical licenses
3. IRB/ERC Approvals
4. IRB/ERC Approved Copies of the Informed Consent Documents
5. IRB/ERC Membership List
6. Roles and Responsibility Log
7. Local Laboratory Information (Name of Laboratory and date)
8. Lab Certifications (Certificate of Accreditation Clinical Laboratory (CLIA) & College of American Pathologists (CAP)
9. Biosample Shipment Certification (Hazmat)
10. Human Research Subject Participation Training Certification
11. Certificates of Confidentiality
12. Subject Screening Logs
13. Monitor Signature Logs
14. Major Correspondence (IRB/ERC, Serious Adverse Events (SAE), DSMB Letters (Project Officers), Site Monitoring Reports, Protocol Amendments, and Protocol Deviations)

A2ALL-2 Core Study Monitoring Log

Site Number/Name: _____

Date of Monitoring Visit	Signature(s) of Monitor(s)	Signature of Site Personnel

A2ALL Core Protocol Subject Screening Log

Subject Initials (First, Last)	Date Approached	Subject Type	Consented Yes or No	Reason not enrolled (# key in footer)	A2ALL-Link ID #	Donor or Recipient	Age	Gender	Race	Ethnicity	Date of Transplant or Donation	Comments

1. Approached-refused; 2. Approached-Dead; 3. Approached – Lost-to-FU; 4. Approached-unresponsive; 5. Not approached-language barrier; 6. Not approached-staffing issues; 7. Inclusion/Exclusion Criteria; 8. Other (specify in comments)

A2ALL Core Protocol Site Signature/Responsibility Form

Site Name/Number: _____
PI Name: _____

Site Personnel (Print)	Signature	Initials	List Responsibilities (#s from list below)	Start Date mm/dd/yyyy	Stop Date mm/dd/yyyy

Study Responsibilities:

1. Obtaining Informed Consent
2. Physical Exam & History
3. Affirmation of Inc. & Excl. Criteria
4. Reporting of SAEs
5. eCRF Completion
6. Data Entry
7. eCRF/Data Corrections
8. CRF Sign Off/Discrepancies
9. Sample Processing
10. Sample Shipping
11. Study Assessments
12. IRB Correspondence
13. Other

Adult to Adult Living Donor Transplantation Cohort Study (A2ALL)

Core Protocol Study Coordinator Training

Welcome & Introductions

- Who are you?
- Who are we?
- Why are we here?

A2ALL

NIH Project Officers

- Averell Sherker, MD – Scientific Advisor for Viral Hepatitis and Liver Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Jill Smith, MD – Director, Clinical & Translational Research in Digestive Diseases National Institutes of Health, NIDDK

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Data Coordinating Center (DCC) Clinical Staff

- Bob Merion, MD – PI and Chair of Steering Committee
- Carl Berg, MD- Consultant
- Anna Lok, MD– Deputy Director
- Akinlolu Ojo, MD– Co-Investigator

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DCC Analytic Staff

- Brenda Gillespie, PhD
- Emily Messersmith, PhD
- Tempie Shearon, MS
- Nate Goodrich, MS
- Abby Smith, BA, MS
- Sarah Forney, MS
- Charlotte Beil, MS
- Lan Tong, MS

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DCC Project Mgmt Staff

- Peg Hill-Callahan, BS, LSW – Project Manager
- Anna Nattie, BA– Project Coordinator
- Jenya Abramovich, BA- Project Assistant
- Gary Xia, BA- Project Assistant

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DCC Clinical Monitoring Staff

- Beth Golden, RN, BScN – Lead Clinical Monitor
- Terri Howell, BS – Clinical Monitor
- Lisa Holloway, BS – Clinical Monitor
- a2all-monitors@umich.edu

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A2ALL Committees & Workgroups

- Steering Committee
  - DCC PI; transplant center PIs; NIDDK
- Project Executive Committee (PEC)
- Publications Committee
- Workgroups
  - Core Protocol
  - Hepatocellular Carcinoma
  - Hepatitis C (HCV)
  - Surgical Innovations
  - Quality of Life (HRQOL)
  - Clinical Immunology
  - Regeneration-Function
  - Donor Pain
- Ancillary studies

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A2ALL Study Website

- www.nih-a2all.org
- General information on the following:
  - Overview of study and participating study sites
  - Active ancillary studies
  - Subject populations and eligibility criteria
  - Publication updates
  - Any news releases
  - Who to contact for further information

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A2ALL Study Website

- www.nih-a2all.org
- 160 user accounts accessible by login and password
- Calendar of events with detailed information.
- Master Documents
  - Has protocols, consent templates, annotated eCRFs, etc.
- All study work group documents
  - Conference call and meeting agendas
  - Meeting minutes
  - Meeting materials
- Study directory and work group information
  - Full contact information for all participants
  - Work group membership lists and email addresses

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A2ALL 2

- Base will be Core Protocol, with sub-protocols either added to Core or developed as stand-alone (separate consent) ancillary studies.
- Current protocol has Health Related Quality of Life (HRQOL), Regeneration, Surgical Innovations, Donor Pain, and HCV protocols rolled in.

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A2ALL 2 Participants

Center	Location	Principal Investigator
Columbia University	New York, NY	Jean Emond, MD
NIH/NIDDK	Bethesda, MD	James Everhart, MD
Northwestern University	Chicago, IL	Michael Abecassis, MD
University of California	San Francisco, CA	Chris Freise, MD
University of Colorado	Aurora, CO	James Burton, MD
University of Michigan*	Ann Arbor, MI	Robert Merion, MD
University of Pennsylvania	Philadelphia, PA	Kim Olthoff, MD
Virginia Commonwealth University	Richmond, VA	Robert Fisher, MD
Lahey Clinic	Burlington, MA	Elizabeth Pomfret, MD
University of Pittsburgh	Pittsburgh, PA	Abhinav Humar, MD
University of Toronto	Toronto, Canada	David Grant, MD

*Data Coordinating Center

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Core Protocol

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6 Aims of the Core Protocol

- Data and sample collection repository
- Health Related Quality of Life (HRQOL)
- To study/characterize the post-transplant outcomes between LDLT and DDLT recipients (RCP)
- Surgical Innovations – pressure & flow measurement plus pre/post op imaging
- Recurrent HCV infection – long-term outcomes in RCPs of LDLT and DDLT
- To study history of pain management & quality of care in pain control in living donors following partial hepatectomy.

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The Logic Path

- As we talk about each protocol, I will describe:
  - Aims/Research Goals/Objectives
  - Study Population(s)
  - Data Sources

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Primary Aim 1

- To collect data and biosamples prior to, during, and after LDLT among all donors and recipients for use by other A2ALL protocols and future studies.

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Primary Aim 1 - Objectives

- To facilitate and inform studies of samples and data collected, thus enhancing the value of this and future investigations.
- To continue contributing to the NIDDK genetics, biosample and data repositories so that current , and future questions regarding liver disease, living donation and liver transplantation can be investigated by A2ALL and external researchers as new technologies, and resources become available.
- To ensure that samples are stored under uniform conditions, and to simplify access by other scientists to samples. Similarly, study datasets will be maintained to facilitate new analyses after the study closes.

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Primary Aim 1 – Study Populations

Original Centers	New Centers
•New Donors	•New Donors
•New Recipients	•New Recipients
•Cohort LDLT RCP	•Gap* Donors
•Cohort Donors	•Gap* LDLT RCP
•Gap* LDLT RCP	•Donors – Prior to Gap
•Gap* Donors	

*Gap Era = Sept. 1, 2009 until Core Protocol site activation.

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Primary Aim 1 – Inclusion Criteria

RECIPIENTS

- Age 18 or older @ consent
- Has had LD identified & accepted and LDLT is planned
- Informed consent (IC) obtained
- Listed for single organ (liver) transplantation

DONORS

- Age 18 or older @ consent
- Has undergone donor evaluation process and was accepted and donation surgery is planned
- IC obtained

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Study Entry

- For new subjects, after donor acceptance, prior to operation.
  - For those sites with a short time period between acceptance and surgery, there needs to be discussion about when is the best time to approach donors who are late in the evaluation process and likely to be accepted.
- For former Cohort and Gap subjects, entry is at next timepoint they would reach post-op (or pre-op if they are very late gap).

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Donor Bio Sample Type	Time Point								
	Pre-Donation	At Donation		Post Donation					
	Shortly Pre-Donation	Just Prior to Resection*	1° Post Resection**	Day 7	Month 1	Month 3	Year 1	Year 2	Year 3	Year 4
Liver Bx - Biorepository		3 CORE BX IN RNA LATER - FROZEN	3 CORE BX IN RNA LATER - FROZEN							
Whole Blood - Genetics Repository	2 EDTA Tubes - AMBIENT†									
Serum - Biorepository	TEN 0.5ML AUQUOTS - FROZEN			TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN			
Plasma - Biorepository	FOUR 0.5ML AUQUOTS - FROZEN				FOUR 0.5ML AUQUOTS - FROZEN	FOUR 0.5ML AUQUOTS - FROZEN	FOUR 0.5ML AUQUOTS - FROZEN			
Nonviable cells (for future cell proteomics) - Biorepository	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN				THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN			
Viable cells resuspended in 10% DMSO & 90% FCS for Flow Cytometry or other studies (such as stimulation) at a future date - Biorepository	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN				THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN			
Whole Blood - DNA Extraction for future study	2 PAXGENE TUBES - FROZEN				2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN			

Recipient BioSample Type	Time Point									
	Pre-TXP	At TXP		Post TXP						
	Shortly Pre-TXP	Back Table	1° Post Reperfusion	Day 7	Week 2	Month 1	Month 3	Year 1	Year 2	Year 3	Year 4
Liver Bx - Biorepository		3 CORE BX IN RNA LATER - FROZEN *	3 CORE BX IN RNA LATER - FROZEN **								
Whole Blood - Genetics Repository	2 EDTA TUBES - AMBIENT †										
Serum - Biorepository	TEN 0.5ML AUQUOTS - FROZEN			TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN	TEN 0.5ML AUQUOTS - FROZEN
Plasma - Biorepository	FOUR 0.5ML AUQUOTS - FROZEN					FOUR 0.5ML AUQUOTS - FROZEN	FOUR 0.5ML AUQUOTS - FROZEN	FOUR 0.5ML AUQUOTS - FROZEN	FOUR 0.5ML AUQUOTS - FROZEN		
Nonviable cells (for future cell proteomics) - Biorepository	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN					THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN RNALater - FROZEN		
Viable cells resuspended in 10% DMSO & 90% FCS for Flow Cytometry or other studies (such as stimulation) at a future date - Biorepository	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN					THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML AUQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN		
Whole Blood - DNA Extraction for future study	2 PAXGENE TUBES - FROZEN					2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN		

A2ALL-2
Health-Related Quality of Life (HRQOL)
Sub-Study Protocol

HRQOL Workgroup

Co-Chairs: ***Mary Amanda Dew, PhD, and*** **Zeeshan Butt, PhD**

Workgroup members:, Daniela Ladner, MD, MPH, Andrea DiMartini, MD
Susan Abbey, MD, April Ashworth, RN, David Axelrod, MD, James Burton MD, Brenda Gillespie, PhD, Susan Holtzman, PhD, Jan Jaeger, PhD, Anastasia Krajec, RN, Mary Ellen Olbrisch, PhD, Elizabeth Pomfret, MD, Mary Ann Simpson, PhD, Norah Terrault, MD, Robert M. Weinrieb, MD

Goals of the Health-Related Quality of Life (HRQOL) Protocol

- **To assess HRQOL domains that (a) have been neglected in A2ALL to date but (b) appear to be adversely affected in living donors.**
- **To assess potential psychological benefits of donation.**
- **To consider HRQOL outcomes not only short-term (1-2 years) post-donation but in the longer-term years.**
- **To employ methodological strategies to overcome poor response rates, missing data, and incomplete follow-up.**

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Overview of Approach

- Build on existing A2ALL HRQOL measures and ARRA-funded validation work
- Deploy strengthened assessment battery in:
  - ***Long-term donor follow-up cohort*: donors previously enrolled in A2ALL from 2002 forward (all >2 yrs at re-contact), plus similar donors from new A2ALL sites. Multi-wave assessments.**
  - ***Prospective donor cohort*: donor candidates enrolled in A2ALL-2, followed to 2 years post-donation.**

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Specific Aims

For both the long-term follow-up and prospective cohorts, the major aims are to determine the prevalence, course, and predictors of poor HRQOL outcomes associated with living liver donation.

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Methods

Long-term donor follow-up cohort

Sample:	Donors from "old" A2ALL centers, 2002 forward (all >2 yrs. at re-contact); similar donors from new centers. Total N ~600.
Study design:	Two-stage design: all donors assessed at baseline. Annual reassessments for 3 years for donors with difficulties/distress (i.e., scores > a pre-determined threshold) on targeted HRQOL domains at baseline. Reassessments of randomly selected donors who do not exceed the threshold.
Procedure:	Re(consent) by individual centers; centralized data collection with telephone surveys of ~30-45 min each; subject reimbursement of $20 per assessment.

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Methods

Prospective donor cohort

Sample:	Donor candidates enrolled in A2ALL-2. Total ~ 375 donors.
Study design:	Prospective, data collected at enrollment (pre-donation), and 3-, 6-, 12-, 24-months post-donation.
Procedure:	Consent by individual centers; centralized data collection involving telephone surveys of ~30-45 min each; subject reimbursement of $20 per assessment.

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Methods

Prospective donor cohort: Assessments

Assessments identical to those employed in long-term follow-up cohort:*

- **Mental Health**
- **Somatic Complaints**
- **Interpersonal Relationships**
- **Financial Concerns**
- **Positive Psychological Outcomes**
- **Generic HRQOL**
- **Demographics**

Additional assessments:

- **Predonation factors:** psychosocial background, donation decision-making, pressure to donate, motives for donating

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*all administered post-donation; some (e.g., financial issues) not assessed predonation

Procedures Issues, HRQOL Surveys

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Procedures: General issues

- Coordinators from each A2ALL-2 site will
  - ➢Obtain consent from study participants
  - ➢Send contact info to their survey research site (NWU)
  - ➢Work with survey research team to troubleshoot problems with contact info or timing of surveys (esp. before donation)
  - ➢Work with survey team and site-specific clinical coordinators to arrange/facilitate care if study participant is deemed to be a danger to self or requests referral for care
- Coordinators from each A2ALL-2 site will not
  - ➢Collect HRQOL survey data
  - ➢Pay study participants for completing HRQOL surveys
  - ➢Re-contact study participants for any HRQOL follow up assessments

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Methods

Long-term donor follow-up cohort: Assessments

- **Mental Health:** depression, anxiety, alcohol use
- **Somatic Complaints:** fatigue, pain, general symptoms, concerns about health
- **Interpersonal Relationships:** with recipient and family
- **Financial Concerns:** financial burdens associated with donation
- **Positive Psychological Outcomes:** general feelings, satisfaction, personal growth
- **Generic HRQOL:** SF-36 v2
- **Demographics:** education, race/ethnicity, etc.

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Procedures: Obtaining consent

- 2 cohorts: Long-term follow-up cohort Prospective cohort
- Each center coordinator will contact eligible individuals and obtain consent
  - ➢Procedures will vary for each cohort
- Centers will maintain files with consent forms; they will not be sent to survey centers

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Procedures: Obtaining consent, prospective cohort

- Two broad approaches
  - ➢**Screen failure approach**
    - Obtain consent at the time of evaluation for donation.
    - If donor is not subsequently approved for donation, it is considered a "screen failure" and consent is void.
    - If donor is approved for donation, assign A2ALL-2 ID.
  - ➢**Enrollment after approval approach**
    - Obtain consent after donor is approved for donation.
    - Assign A2ALL -2 ID.
- Use approach that allows for sufficient time to conduct pre-donation HRQOL telephone survey
  - ➢Under ideal circumstances, ~7-10 days before surgery would be optimal.
  - ➢Anticipated surgery date will be required so that interviewers are aware of amount of time available.

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Procedures: Obtaining consent, long-term follow-up cohort

-
  - Obtain HIPAA authorization.
  - Contact all donors > 2 years post-donation (since 2002) and obtain consent. Do so within 1 month (either way) of anniversary of donation.
  - Obtain and assign new A2ALL -2 ID number.
  - Complete medical records review for required data on donor at time of donation and on recipient since donation.

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Procedures: Sending data to survey center

- Log in to secure, password-protected website for your survey center (NWU)
- Provide standard information
  - Name, address, all telephone numbers, email address, date of donation (or anticipated donation), A2ALL-2 ID
  - Return to website to provide actual date of donation for donors in prospective cohort
  - Critical issue for prospective cohort: short turn around time between consent and donation will make timely communication essential

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Procedures: Other responsibilities linked with general A2ALL activities

- Complete medical records reviews for donors and recipients
  - ➢ Prospective cohort: requirements to be delineated through Core Protocol and other sub studies
  - ➢ Long-term HRQOL follow-up cohort
    - extraction of data at time points closest to the time points of collection of HRQOL survey data
    - extraction of medical records elements on donors and recipients at time of donation

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Procedures: Collection of survey data

- Computer-assisted telephone surveys (CATI) using standard software.
- Separate database for maintaining contact info and tracking/scheduling/monitoring completion.
- Both CATI survey data and tracking database have firewalls and store data in encrypted form.
- Survey centers use a range of other security procedures to protect and manage data.
- Tracking database will yield quarterly progress reports to the DCC. Pitt will monitor progress weekly.

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Procedures: Training/monitoring of interviewers

- Certified in HIPAA, Research Fundamentals, Ethics and Human Subjects Protections.
- Trained in general interviewing principles and will be trained on issues relevant to A2ALL-2 HRQOL surveys.
- Trained in the event that study participants indicate they are thinking of harming themselves (or others).
- Overseen by CATI supervisor, working with A2ALL-2 coordinator and local co-investigators.

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Procedures: Two-way conversation with A2ALL coordinators

- Dr. Dew (at Pitt) is available for additional telephone conference calls with coordinators.
- HRQOL survey coordinators will also be available for individual calls (Elizabeth Rauch @ NWU).
- Elizabeth will be in frequent contact with coordinators at each site, especially when enrolling the prospective cohort due to timing issues.
- The HRQOL Workgroup wants to know when procedures do or do not work; they will modify accordingly.

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Web Portal at Northwestern University

www.assessmentcenter.net

- Log into demo site, and register a new subject .

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Surgical Innovations Protocol Objectives

- 1: To establish the normal hepatic blood flow and portal compliance in the human liver.
- 2: To determine the hepatic flow and pressure, and graft size and function and clinical outcomes in LDLT for recipients.
- 3: To establish the benefit, if any, of portal flow modulation interventions on hepatic compliance, and functional and clinical outcomes.

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Intraop Details

- Using Transonic HTE322 flowmeter, pressure and blood flow rates through the hepatic artery, and portal vein are measured in the recipient.
- The surgeon will take 3 measurements (once readings have stabilized) of each vessel at each intraoperative time point (machine will print out Min., Max., and Mean). These print outs should include the subject study ID #, and kept as source documents.
- Surgical innovations group have developed donor, and recipient intraop worksheets to take into the OR.

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Intraop Details (cont.)

- The surgeon performing the transplant or donation is to complete (within 24 hours) the appropriate intraop form sign and date.
- The information from the intraop worksheets and readings from the print outs are entered into the database.
- The print outs from the flowmeter should be scanned and attached to the appropriate intraop worksheet. All intraop worksheets, print outs, and scanned/copied documents are to be kept in the subject study binder.

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HCV Study

Primary Aim 5: To compare the long-term histological outcomes in recipients of LDLT and DDLT with recurrent HCV infection

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Study Population

Inclusion Criteria

- CONTINUING CENTERS: LDLT and DDLT recipients
  - enrolled in Cohort or Core Gap (3 years post-op)
  - with evidence of HCV at transplant

Exclusion Criteria

- Refused Cohort study
- Documented Sustained Virologic Response (SVR) prior to TXP
  - Undetectable HCV RNA at least 6 months post-treatment
- Co-infection with Hep. B (HBsAg+)
- Co-infection with HIV
- Receipt of a graft from an HCV-infected donor
- Died less than 90 days post-op
- Re-TXP less than 90 days post-op
- Was one of the first 20 adult to adult LDLTs performed at the center

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Continuing Sites – eligible subjects who are already in Core

- Must be at least 3 years post transplant, and meet all of the eligibility criteria on the HCV Subject Flow eCRF
- HCV indicated as a diagnosis in the Cohort data base (BioDBx) on the RCP @ DNR Eval eCRF
- Some fields that were completed in Cohort will be pre-populated in the HCV TXP Information eCRF and HCV Advanced Disease eCRF.

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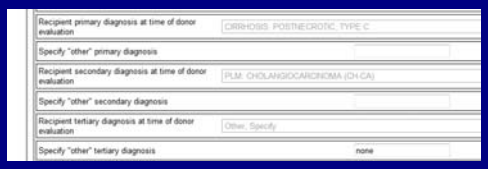
RCP @ DNR Eval (BioDBx)



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Continuing Sites – eligible subjects who were not eligible for Core

- These subjects will be considered "HCV Only"
- Includes dead, and re-transplanted subjects (if death or re-transplant occurred more than 90 days post-op)
- Will be uploaded into A2ALL-Link, and will appear on your subject list
- Fields that were already filled out in Cohort will be pre-populated in A2ALL-Link
- Dead, re-transplanted and lost to follow-up subjects will have data collected via waiver of consent

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New Sites

- Eligible subjects with HCV should have "HCV" checked "Yes" in Question A5 on the RCP Study Entry eCRF

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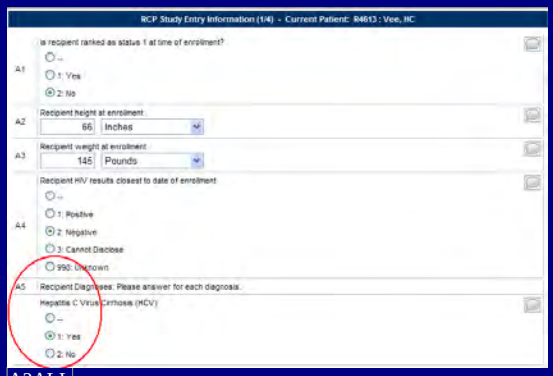

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New Sites

- Eligible subjects will be entered as new subjects, designated "HCV Only" in the database (unless Core-eligible Gap)
  - Gap DDLT Recipients would be HCV-only at new sites
- Dead, lost to follow-up and re-transplanted subjects will have data collected via waiver of consent

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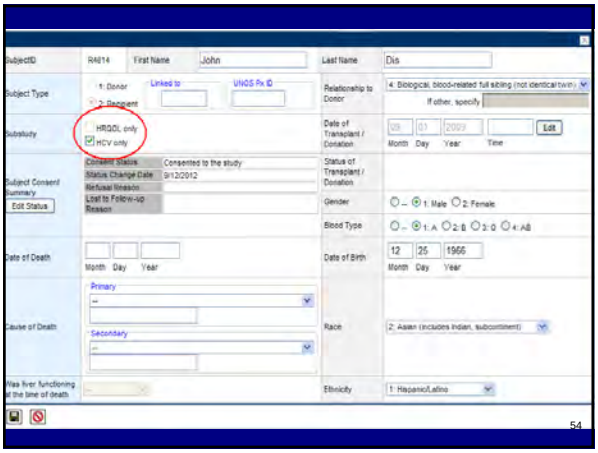

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HCV Only

- eCRFs for these subjects will appear in the tasks list once you've checked the "HCV Only" box **and** entered the consent status as "waiver of consent" (dead, and lost to follow-up)
- Note that hospitalization and complication eCRFs will show up for all subjects, but should not be completed for HCV-only subjects

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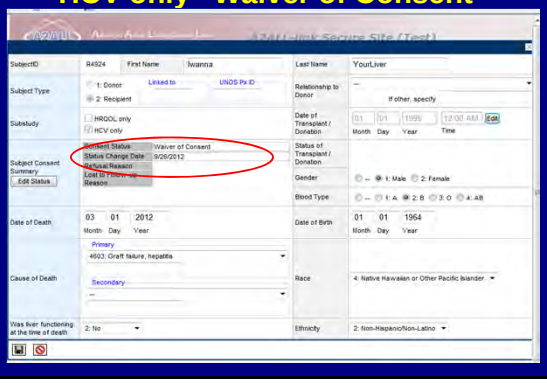
HCV only "Waiver of Consent"



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Consent

- Core Subjects – consent to this sub-study is part of the Core Protocol Recipient study consent* and was approved as part of Amendment 2
- HCV – only Subjects – should sign the HCV – only consent (if applicable) that was approved as part of Amendment #2

*Core subjects not in the HCV substudy need not be reconsented due to Amendment 2

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HCV Subject Flow eCRF

- Will appear for all potentially eligible subjects
- First section (Questions A-1 to A-6) reconfirms eligibility. If you answer "Yes" to any of these questions, the subject is not eligible and no additional HCV eCRFs will be displayed
- Section B determines what eCRFs are to be completed for the HCV sub study, if the subject meets the eligibility criteria (determined in Section A)

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HCV eCRFs

- All eligible subjects get the following eCRFs populated in their task list:
  - HCV Subject Flow
  - HCV TXP Info
  - HCV Study Info
  - HCV Advanced Disease
- All subjects will need to have a Bx eCRF completed for each post-Txp Bx.
- The Elastography eCRF will generate for those subjects at sites where this is applicable (UCSF, Toronto and NWU).

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Post TXP Bx Results eCRF

- This should be filled out for each post-TXP Bx that occurs on <u>ALL</u> RCPs
- Select the HCV Protocol Bx for:
  - A past biopsy that showed cirrhosis (B2 =yes on HCV Study Subject Flow eCRF)
  - A biopsy done within the last 12 months (B3 =yes on HCV Study Subject Flow eCRF)
  - A prospective biopsy, (B4=yes on HCV Study Subject Flow eCRF)

A2ALL

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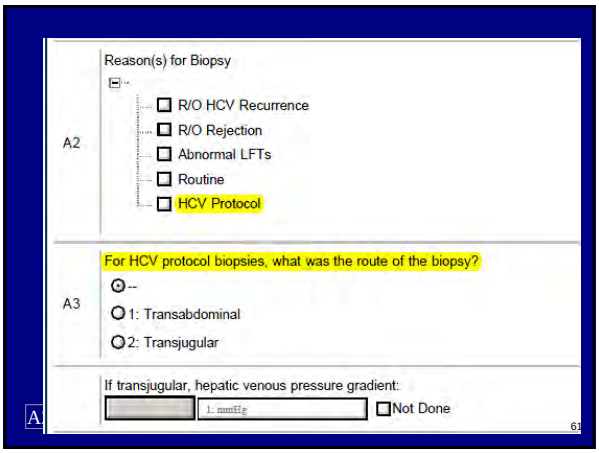
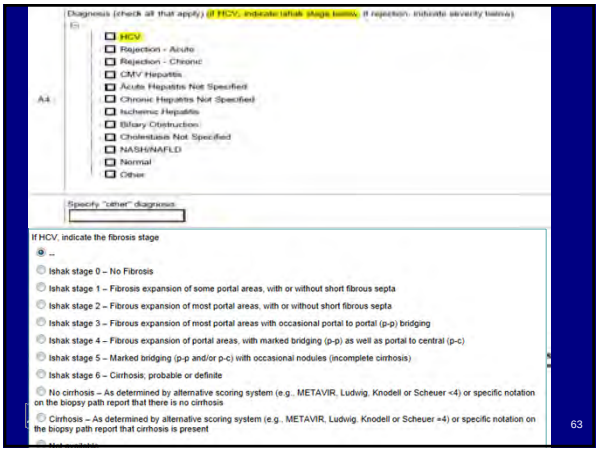


Bx Results

- Review the HCV Biopsy report and indicate on the Post Txp HCV Bx eCRF the diagnoses and Ishak Fibrosis Stage (see various categories).
- If an Ishak Score is not easily determined according to the report and/or PI review of the report, a re-read from your pathology dept. should be requested.

A2ALL

62



Section B

– Post-Txp Bx Report

A2ALL

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Section B

- B1 = No (died or re-transplanted more than 90 days from index graft)
  - HCV Txp Info
  - HCV Study Info
  - HCV Advanced Disease

A2ALL

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Section B

- B1 = Yes (alive)
- B2 = Yes (prior evidence of cirrhosis)
- B2-1 = Clinical evidence (source=clinical)
  - HCV Txp Info
  - HCV Study Info
  - HCV Advanced Disease

A2ALL

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Section B

- B1 = Yes (alive)
- B2 = No (no prior evidence of cirrhosis)
- B3 = Yes (had Bx within past 12 months)
  - HCV Txp Info
  - HCV Study Info
  - Post-Txp Bx Report
    - If Ishak fibrosis score was not noted on previous Bx, then it will have to be re-read
  - HCV Advanced Disease

A2ALL 67

Section B

- HCV Txp Info
- HCV Study Info
- HCV Elastography Report (if available) or HCV Advanced Disease

A2ALL 68

Section B

- B1 = Yes (alive)
- B2 = No (no prior evidence of cirrhosis)
- B3 = No (no Bx within past 12 months)
- B4 = Yes (will get ≥ 3 yr Bx)
  - HCV Txp Info
  - HCV Study Info
  - Post-Txp Bx Report
  - HCV Elastography Report (if available)

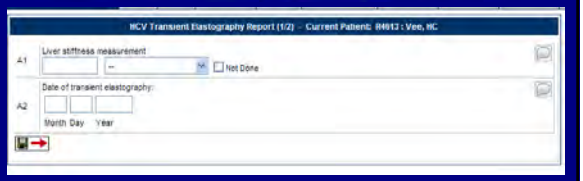
A2ALL 69

Elastography

- Elastography or Fibroscan is available at 3 sites: UCSF, Toronto, and Northwestern
- Elastography will be performed on subjects at those sites who:
  - Won't get a Bx due to consent or safety reasons
  - Do get a protocol Bx (paired elastography done within 90 days of the Bx to validate the use of Fibroscan to Dx cirrhosis)
- Complete the HCV Elastography Report eCRF for subjects that undergo Fibroscan

A2ALL 70

HCV Elastography Report eCRF



A2ALL 71

Liver Bx

- All eligible subjects will be approached for liver Bx unless they have:
  - Re-transplantation
  - Clinical evidence of decompensated cirrhosis
  - Cirrhosis documented on previous Bx
  - Bx performed within the last 12 months
  - Coagulopathy precluding a safe Bx

A2ALL 72

Scheduling

- If subject agrees to have a Protocol Bx (≥3 Year post txp, based on the answer provided in Section B of the Subject Flow eCRF)
- Go to the Task List in A2ALL- Link
- Choose Post-TXP Year 3+ HCV Visit
- Enter appointment info and save

A2ALL

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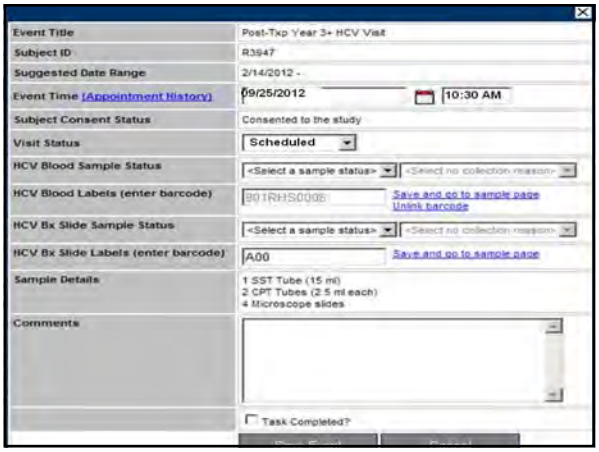

Biosamples

- **Collected at time of Bx** (Amendment 2 consent version, or at anytime with Amendment 3 consent)
- **1 SST tube**
  - 10 serum aliquots
- **2 CPT tubes or green top tube**
  - 4 plasma aliquots
- **2 EDTA**
  - Whole blood for Genetics Repository <u>if not previously collected</u> (use extra sample labels and check "Whole Blood for Genetics")

A2ALL

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Extra Slides for Central Read

- Link slide labels at the same time of Biosample labels; each has its own link
- 4 slides
  - 1 H&E
  - 1 Trichrome
  - 2 Unstained
- Send to Toronto quarterly (next shipment due to be sent in Sept. 2013 as June shipment not sent) during the first week of that month. Shipping began in December, 2012
- Use the pre-printed slide labels, and biosample labels provided by the DCC

A2ALL

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HCV TXP Info eCRF

- Complete for all eligible subjects
- Former Cohort subjects will have some data fields pre-populated if answered in the Cohort database
- All questions in Sections A-C should be answered retrospectively for status at TXP
- Section D asks for immunosuppression info at 1 year post-transplant.

A2ALL 79

HCV TXP Info eCRF (cont.)

- Section A – collects BMI components, dialysis and HCC Dx
- Section B – collects info about the donor
  - If LDLT and donor info is in Cohort, parts of this section will be pre-populated
  - If DDLT information will be collected regarding gender, ethnicity, race, type, cause of death and Donation After Cardiac Death (DCD) status.
  - Cold and warm ischemic times are based on the donation operation
- Section C – lab values at TXP (pre-op)
- Section D – Immunosuppression regimen at one year post-txp

A2ALL 80

HCV Study Info eCRF

- Date of Cirrhosis Assessment:
  - For subjects who underwent protocol Bx = Date of Bx
  - For subject with previously documented cirrhosis=Date of Bx (1st showing cirrhosis)
  - Alive without re-TXP = Advanced Disease CRF date
  - Alive with re-TXP = Re-TXP date
  - Dead without re-Txp = Death date
  - Dead with re-Txp = Re-Txp date

A2ALL Note: Timeframe = Date of transplant to date of cirrhosis assessment 81

Section A – Post TXP Follow-up

- QA2 – collects information about post-txp HCV treatment and its result
- QA3 – collects information about rejection episodes and treatment
- QA4 – collects information about CMV viremia
- QA5 – collects information about biliary complications

A2ALL 82

Section B – Status @ Assessment

- Time of assessment = date of contact
- Section B collects data about the subject's clinical status and immunosuppression regimen

A2ALL 83

Section C - Labs

- Collects lab values closest to the time of cirrhosis evaluation (date of assessment in Section A)

A2ALL 84

HCV Advanced Disease eCRF

- QA1 – Date of advanced disease assessment = date you complete the eCRF
- The rest of the eCRF asks you to document signs, Sx and lab values pointing to advanced disease, and the dates of occurrence
- QA11 & A12 – Investigator assessment of whether subject met criteria for having advanced liver disease due to recurrent HCV (utilize the Advanced Disease Tool located in the MOO V1.4 Appendix T)
  - Create an anecdotal note to file for source documentation

A2ALL 85

Donor Pain Protocol

Primary Aim 6: To understand the history of pain management, and to measure quality of care in pain control in living donors following partial hepatectomy.

A2ALL 86

General Information

- Pain Survey is administered to prospective donors by the study coordinator 48-72 hours post-op
  - Goal is to administer as close to 48 hours as possible

A2ALL 87

Consent

- Consent for this substudy is contained in the Core study donor consent that was part of Amendment 2.0

A2ALL 88

Pain Ancillary Study

- Inclusion Criteria:
- Adult living liver donors
- Consent obtained prior to donation surgery

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Pain Ancillary Study

- Exclusion Criteria:
- Unable to obtain consent prior to donation surgery
- History of chronic pain
- History of narcotic use (routine scheduled narcotic use for treatment of a pain disorder diagnosed and treated by a physician)
- Medically unstable at 48 hrs post-donation surgery
- Language barrier

A2ALL

Study Population

Inclusion Criteria
- Adult living liver donors

Exclusion Criteria
- History of chronic pain
  - Chronic or intermittent pain for at least 3 months
- History of narcotic use
  - (routine scheduled narcotic use for treatment of a pain disorder diagnosed and treated by a physician)
- Medically unstable at 48 hours post-donation surgery
- Language barrier

A2ALL 91

Survey Administration

- You may either print the form, and circle the subject's answers or fill the form out electronically on a laptop
- Enter the subject's A2ALL ID# on every page
- Enter the date, and time of the first attempt to administer the survey

A2ALL 92

Cover Letter

- Read the cover letter to the subject
- Obtain the subject's verbal permission to proceed with the survey administration

A2ALL 93

Donor Pain Cover Letter V3.2

A2ALL 94

Sedation Score

- Before administering the survey, assess the subject's sedation score:
  - 0 = Fully Awake
  - 1 = Light sedation, largely aware of self/surroundings. Mildly sleepy.
  - 2 = Moderate sedation, slightly aware of self/surroundings. Somnolent but easily aroused.
  - 3 = Deeply sedated, unaware of self/surroundings.
  - 4 = General anesthesia, patient is unconscious.

A2ALL 95

Sedation Score

- If the subject scores higher than 2, you should not administer the survey but try again later
- Enter date and time of second attempt and the new sedation score

A2ALL 96

Type of Pain Management

- Document all types of pain medication routes, utilized for the subject post-operatively
- Do not enter name of the medication on the survey

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Survey Administration

- Read each question and explain the scale
- Record the subject's answers
  - For the 0-10 scale questions, choose only one number (NOT 7.5 as an example)
- For QP11: if the subject indicated use of non-medical methods of pain relief, check all that apply
- Don't forget to thank the subject!

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Donor Pain Survey Version 3.2

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Unable to Administer Survey

- If you are unable to administer the survey within the window, go to A2ALL-*Link*, and complete Question C1 on the DNR at 1 week post-op eCRF
- Document the reason why the survey wasn't administered. Choices are:
  - Sedation score ≥ 3 at each attempt
  - Subject refused
  - Subject medical/emotional issues precluded survey administration
  - Administrative/staffing issues

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A2ALL-*Link*

- On the Donor Post-op at One Week eCRF, answer question C1

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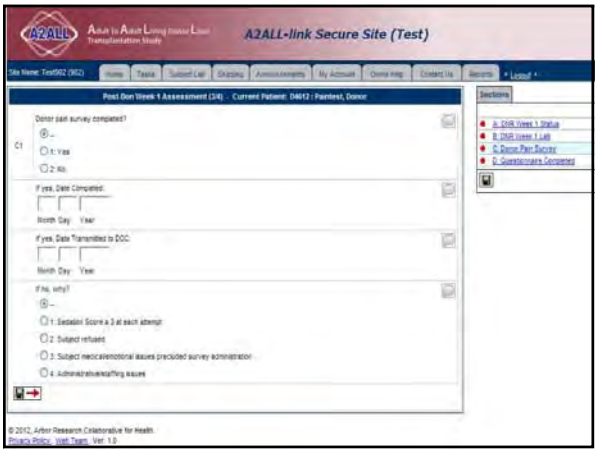

Documentation – Paper Forms

- Either scan the form or bring up the fillable PDF on your computer and transcribe the information from the paper form to the electronic version
- Save the original paper form as a source document in the subject's research file.

A2ALL

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Saving Surveys

- Make a folder in a secure location on your computer called, "A2ALL Donor Pain Surveys," with two subfolders titled "Transmitted" and "Untransmitted"
- Save scanned or electronically completed surveys as PDFs in the Untransmitted folder

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File-Naming Convention

- Site ID_A2ALL Subject ID_Date of Administration_Your Initials
- Example: 310_D1234_092312_PHC

A2ALL

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Transmission to DCC

- On the 15th of each month, transmit all untransmitted forms by attaching them to one or more emails addressed to: a2all-painsurveys@umich.edu
- Utilize the Report function in A2ALL-*Link* to identify untransmitted surveys
- Move the now transmitted PDFs to your "Transmitted" folder

A2ALL

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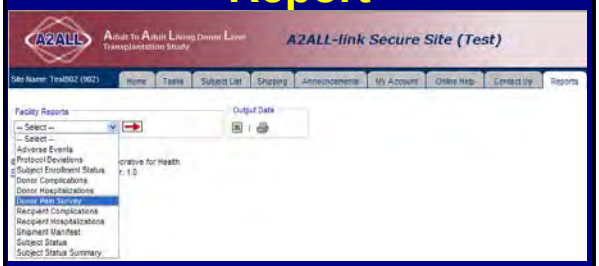
Report



Go to the Reports tab in A2ALL-*Link*, and choose the Donor Pain Survey Option

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- Export the report to Excel, choose "Auto filter", and sort by:
  - Donor Pain Survey Completed = Yes
  - Date Transmitted to DCC = Blank
- This will show you all of the completed surveys that have not been transmitted to the DCC. This should match all of the saved surveys in your "Not Transmitted" folder
- After you send the completed surveys to the DCC, go to the DNR Week 1 Post-op eCRF, and put the date sent in Section C1 and save the form
- Move the transmitted surveys to your "Transmitted" folder.

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Core Protocol Amendment #3

- IRB package sent to sites on May 2, 2013.
- NWU already IRB approved
- **Summary of changes**
- Housekeeping changes
- Primary Aim 3, follow-up of Long-term donors changed to follow-up for three years after baseline assessment at time of re-contact (based on early review of certain donors who scored positive on certain threshold questions).

A2ALL 109

Summary of Changes (cont.)

- Primary Aim 4
  - Removed ascites output as a data element since we already collect drain output which includes ascites.
- Primary Aim 5
  - Added "LDLT was one of first 20 cases at site" as an exclusion criteria.
  - All subjects will have the Advanced Disease eCRF completed.
  - Clarification that GAP subjects who meet inclusion criteria are eligible.

A2ALL 110

Summary of Changes (cont.)

- Primary Aim 5
  - Subjects who are re-transplanted, deceased or lost-to-follow-up will have chart review conducted under a waiver of consent.
  - GAP-era Core subjects who reached a study endpoint after consenting to the Core Study, will have their charts reviewed under a waiver of consent.
  - Collection of bio-samples can be collected from all subjects at any time after HCV sub-study entry
  - Clarification and additions regarding what Bx slides will be sent for central reading at the University of Toronto

A2ALL 111

Summary of Changes (cont.)

- Primary Aim 6
  - Inclusion and exclusion criteria were updated to eliminate the "consent obtained at least 48 hours prior to donation surgery" criteria.
  - Appendix F was updated to include the current version of the Donor Pain Survey.
- Appendix D updated to include GAP subjects into HCV sub-study.

A2ALL 112

Informed Consent

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Approach

- It is critical that site personnel put careful thought in how to maximize subject accrual and retention.
- Integration of research interventions into existing clinical flow will enhance acceptance, and cooperation with colleagues, as well as minimizing wasted time and frustration for the subject.

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Study Procedures vs. Standard of Care

- Remember when talking to subjects, and when thinking about the study, this study is primarily observational, and we're simply collecting data on what occurs normally in the course of clinical care.
- Most of what we collect is Standard of Care (SOC) in many facilities.

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Identification of Potential Subjects

- How do you know:
  - Who is being considered to receive or donate LDLT?
  - Who has been accepted?
  - When the operation is scheduled?

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Timing

- When is the best time to approach a subject?
- How much time do you need to explain the study and obtain informed consent (IC)?
- Where will the consenting process take place?

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Informed Consent

- Prior to signing the current IC, there should be a full description, discussion of study procedures, and associated risks.
- A signed/dated IRB, DCC, and NIDDK-approved informed consent document must be obtained from each subject.
- The consent needs to be signed prior to any study procedures being performed.
- Signature needs to be witnessed if required at the site.
- The person obtaining IC also needs to sign, date, and write an anecdotal note to file on the informed consent process.
- Do NOT deface the consent, any changes need to be IRB approved.

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Communication

- Is the key
- Make sure you discuss the study with clinical staff who will also be interacting with your subjects.

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Risks – All Subjects

- Phlebotomy: syncope, pain, infection, phlebitis, and hematoma. All blood will be drawn by qualified personnel, and subjects monitored for any complications.
- Intraop biopsy: bleeding, damage to allograft and rarely death. Severe complication rate is less than 0.1% and all biopsies will be conducted by trained personnel.

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Risks – All Subjects

- Pressure & Flow Measurements – risk of tearing the vessel requiring repair by the surgeon.
- MRI: Claustrophobia or restlessness. All subjects will be informed of the nature of the procedure, and will be allowed to stop if they become too uncomfortable.

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Consent Status Definitions

- Consented to Full Study
- Refused Biosample Repository
- Refused Genetics Repository
- Refused both Biosample and Genetics Repository – agreed to everything except genetics and biosample collection and storage
- Dead – use when a consented subject dies during the course of the study
- Approached - Dead
- Approached - Lost to Follow-up/Unresponsive – unable to contact former subjects through letters or phone calls (at least three valid attempts)
- Approached – Refused Consent
- Lost to Follow-up/Unresponsive - use when consented subjects misses 3 or more consecutive scheduled visits, this status is generated through A2ALL-Link
- Removed - Reached Study Endpoint – use when a consented subject reaches an endpoint prior to completing all study visits. Examples include:
  - Donation or TXP surgery aborted
  - Recipient gets DDLT
  - Recipient no longer eligible for LDLT
- Withdrew Consent – use when a consented subject withdraws consent
- Subject Entered by Mistake
- HRQOL only-for use by donors who are not enrolled into the Core protocol
- HCV only-for HCV only subjects, not enrolled into the Core protocol (new sites)
- Waiver of Consent-to be used for HCV only subjects who are dead, or lost to follow-up

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Consent Status Definitions Continued : former A2ALL Cohort Subjects

- Approached – dead – use when a former Cohort subject's death is discovered when you try to contact for consent.
- Approached – Lost to Follow-up/Unresponsive – use when you have exhausted all routes to contact a former Cohort subject for consent. Document Lost to Follow-up or Unresponsive reason (if known) on screening log.
- Approached – Refused Consent – use when you approach a former Cohort subject for consent, and they refuse all aspects of study (document reasons for consent refusal on screening log).

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Data Definitions

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Data Elements

- Specimens collected from subjects, processed at site, and stored in NIDDK Biorepository.
- Clinical Data – reported on electronic CRFs (eCRFs) in A2ALL-*Link* database.
- Demographic Data – reported in the database.

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Data Module Review

Donors

- Demographics
- Intraop
- Post Donation Assessments
- Hospitalizations
- Complications

Recipients

- Demographics
- RCP Study Entry Info
- Intraop
- Post-TXP Assessments
- Hospitalizations
- Complications
- Bx Report
- HCC Explant
- HCV

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Donor Bio Sample Type	Time Point								
	Pre-Donation	At Donation		Post Donation					
	Shortly Pre-Donation	Just Prior to Resection*	1° Post Resection**	Day 7	Month 1	Month 3	Year 1	Year 2	Year 3	Year 4
Liver Bx - Biorepository		3 CORE BX IN RNA LATER - FROZEN	3 CORE BX IN RNA LATER - FROZEN							
Whole Blood - Genetics Repository	2 EDTA Tubes - AMBIENT?									
Serum - Biorepository	TEN 0.5ML ALIQUOTS - FROZEN			TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN			
Plasma - Biorepository	FOUR 0.5ML ALIQUOTS - FROZEN				FOUR 0.5ML ALIQUOTS - FROZEN	FOUR 0.5ML ALIQUOTS - FROZEN	FOUR 0.5ML ALIQUOTS - FROZEN			
Nonviable cells (for future cell proteomics) - Biorepository	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN				THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN			
Viable cells resuspended in 10% DMSO & 90% FCS for Flow Cytometry or other studies (such as stimulation) at a future date - Biorepository	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN				THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN			
Whole Blood - DNA Extraction for future study	2 PAXGENE TUBES - FROZEN				2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN			

Data Source - Donor eCRFs

- Health Related Quality of Life (HRQOL)
- Intraop
- Hospitalizations
- Complications – list of 47 study tracked complications
- Condition @ Wk. 1, M1, M3, Y1, and annually – vital status and lab results

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DNR Data Elements* (collected on eCRFs)

- Intraoperative Data

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*In addition to what is being collected in the Core Protocol

Recipient BioSample Type	Time Point									
	Pre-TXP	At TXP		Post TXP						
	Shortly Pre-TXP	Back Table	1° Post Reperfusion	Day 7	Week 2	Month 1	Month 3	Year 1	Year 2	Year 3	Year 4
Liver Bx - Biorepository		3 CORE BX IN RNA LATER - FROZEN *	3 CORE BX IN RNA LATER - FROZEN **								
Whole Blood - Genetics Repository	2 EDTA TUBES - AMBIENT †										
Serum - Biorepository	TEN 0.5ML ALIQUOTS - FROZEN			TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN	TEN 0.5ML ALIQUOTS - FROZEN
Plasma - Biorepository	FOUR 0.5ML ALIQUOTS - FROZEN					FOUR 0.5ML ALIQUOTS - FROZEN	FOUR 0.5ML ALIQUOTS - FROZEN	FOUR 0.5ML ALIQUOTS - FROZEN	FOUR 0.5ML ALIQUOTS - FROZEN		
Nonviable cells (for future cell proteomics) - Biorepository	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN					THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN		
Viable cells resuspended in 10% DMSO & 90% FCS for Flow Cytometry or other studies (such as stimulation) at a future date - Biorepository	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN					THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN	THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN		
Whole Blood - DNA Extraction for future study	2 PAXGENE TUBES - FROZEN					2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN	2 PAXGENE TUBES - FROZEN		

Data Source - RCP eCRFs

- Enrollment – labs and clinical info
- Pre-op – labs and pre-op imaging recorded on the intraop form
- Intraop
- Hospitalizations – For gap recipients, and donors complete hospitalizations beginning with the transplant or donation admission and continue through study. Only those admissions ≥ 24 hours are considered hospitalizations.
- Complications – list of 48 study tracked post-TXP complications
- Bx Pathology Report – for-cause Bx
- Condition @ Wks. 1& 2, M1, M3, Y1 and Annually – vital status and lab results

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RCP Data Elements* (collected on eCRFs)

- Pre-op – MRI/CT measuring liver & spleen volume.
- Intraop
  - Portal pressure & flow measurements,
  - Central venous pressure (CVP)
  - Mean arterial pressure (MAP)
  - Cardiac output
- Early Post-op Period (W1, W2, M1) –
  - Portal vein flow via Doppler on Day 1
  - Abdominal drain(s) output
  - Encephalopathy grade

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*In addition to what is being collected in the Core Protocol

Data Entry Expectations :

- occurrence verification
- 48 hours for sample collection status and visit status
- 3 weeks for completion of electronic case report forms (eCRFs)

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Source Documentation

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Source Documentation Includes the following:

- **Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, microfilm or magnetic media, x-rays, copies or transcriptions certified after verification as being accurate and complete).**

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A2ALL

Documentation

- **Site personnel must document in the subject's medical record that:**
  - **The subject has signed the informed consent**
  - **Met enrollment criteria, and enrolled into the A2ALL-2 Core Protocol study**
  - **DCC provides a form for this, and you can find it in the Manual of Operations (MOO) Appendix U**
- **The signed informed consent document should be maintained in the following locations:**
  - **The original form is placed in the subject's research file**
  - **A copy is to be placed in the subject's medical chart**
  - **Subject or legal guardian will receive a copy**

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Source Documentation Tools for A2ALL-2:

- **The DCC provides the sites with a source documentation tool (Intra-op Worksheet) for the collection of Intra Operative Data. The source needs to be signed, and dated (within 24 hrs) by the surgeon performing the transplant or donation procedure.**
- **Source documentation for verification of consent is required. This documentation is completed by the staff person (IRB approved) obtaining consent, and should be filed along with the consent form in the subject's study file.**

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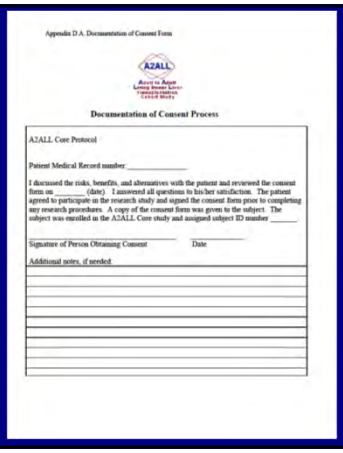

Appendix D.A. Documentation of Consent Form

A2ALL

Documentation of Consent Process

A2ALL Core Protocol

Patient Medical Record number: _____

I discussed the risks, benefits, and alternatives with the patient and reviewed the consent form on _____ (date). I answered all questions to his/her satisfaction. The patient agreed to participate in the research study and signed the consent form prior to completing any research procedures. A copy of the consent form was given to the subject. The subject was enrolled in the A2ALL Core study and assigned subject ID number _____

Signature of Person Obtaining Consent _____ Date _____

Additional notes, if needed:

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Intraop Worksheets

- Donor Intraop Worksheet
- Recipient Intraop Worksheet

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Source Documentation

- Remember to document conversations made with your research subjects.
- If you make a phone call to inquire about an ongoing complication or a study visit that was missed, document the conversation in a note to file, and place in the subject's research file.
- Remember: If it's not documented, it didn't happen.

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A2ALL-*Link* Demonstration:

- Please refer to A2ALL-*Link* User Guide V1.7 for step by step instructions

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A2ALL-*Link* Demonstration Topics

- Log-In
- Namekey
- Announcements
- Help
- Adding a New Subject
- Old Subjects
- Consent Status
- Calendaring
- Sample Collection
- Sample Documentation
- Filling Out eCRFs
- Report Function

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Sample Collection/Demonstration:

- Collection
- Handling
- Processing
- Labeling
- Storage
- Shipping
- Tracking

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A2ALL-2 CORE PROTOCOL

SAMPLE COLLECTION

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Collection & Processing

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NIDDK Repository Info

- Genetics Repository – Fisher BioServices will utilize their Core DNA Lab to extract the DNA from the EDTA tubes, and send to the NIDDK Biosample Repository for storage. Sites collect a single blood draw from donors and recipients, and are shipped ambiently.
- NIDDK Biosample Repository – sites will send samples of blood, and liver tissue from specified time-points in the protocol. All samples will be frozen and batch-shipped monthly.

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Repository Site IDs

Returning Centers	
Columbia	310
NWU	311
Penn	312
Colorado	313
UCSF	315
VCU	318

New Centers	
Lahey	840
Pitt	841
Toronto	842

These site identifying numbers are used in conjunction with repository communication.

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Materials

- DCC will provide:
  - pre-printed bar-coded sample labels to each site on a regular basis.
  - 2 ml vials for serum aliquots.
- Fisher will provide: shipping materials for all specimens (including dry ice containers).
- Your site will provide: blood collection tubes and needles for blood collection, as well as reagents for processing and storage of cells.

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Tubes & Yields

After processing, the following tubes yield the following products:

- SST – serum aliquots
- CPT – plasma, viable and nonviable cells

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Whole Blood – Genetics Repository

- Ethylene diamine tetra-acetate (EDTA) Tubes – Whole Blood.
- Collect 2 tubes for storage of genetic material.
  - Draw to capacity
- Gently invert 8-10 times to mix solution with blood.
- Ship to Fisher BioServices within 48 hrs. Do not freeze.

EDTA TUBE

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SST

- Serum Separator Tube – yields serum
- Draw to capacity
- Gently invert 8-10X
- Centrifuge for 10 minutes at 1500-1800 RCF.
- Aliquot serum – 0.5ml into 10 cryovials
- Freeze in -20°C, -80°C is acceptable.

SST TUBE

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Whole Blood – Collected in 2 PaxGene Tubes

- Draw 2.5ml of blood.
- Invert tube 10X immediately after draw.
- Initial freeze -20°C for 24 hours then transfer to -80˚C.
- Store upright in wire or plastic rack until shipped.

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Plasma & Cells (viable & nonviable)

- All are collected in 2 CPT tubes
- Draw 8ml blood per tube
- Invert 10X
- Keep @ room temp

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Processing CPT Tubes

- Centrifuge ASAP, but no later than 2 hours after draw. Spin for 20 minutes at 1700 RCF (relative centrifugal force).
- The centrifugation process will cause the plasma to separate from the mononuclear cells and platelets.
- The next step will be to aliquot the plasma from the tubes.

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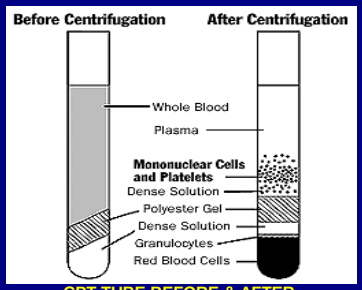

CPT TUBE BEFORE & AFTER CENTRIFUGATION

After centrifugation, each tube should have 2ml of plasma. Using a transfer pipette, carefully transfer 0.5ml of plasma into 4 labeled containers. Freeze at -20˚

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Questions

- Does anyone see any problems with the logistics of collecting the plasma?
- Is the 2 hour time limit a problem? What about for the OR samples?
- Does everyone have access to and know how to use a transfer pipette?
- How many sites have Clinical Research Units who could draw and/or process the biosamples? What would it cost?
  - UM charges $6.16/sample for plasma and $12.12/sample for buffy coat processing
  - Will this require two venipunctures?

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Collecting non-viable cells from CPT Tube #1

1. Recap the CPT tube with the stopper and invert the tube 10X
2. Pour off the cell/plasma mixture into a 15ml blue-cap tube
3. Add PBS (phosphate buffered saline) to bring volume to 15ml
4. Cap tube, and mix cells by inverting 5X
5. Centrifuge for 15 minutes at 300 RCF
6. Aspirate as much supernatant as possible without disturbing the cell pellet
7. Resuspend the pellet
8. Add PBS to bring volume to 10ml
9. Cap tube and mix cells by inverting 5X
10. Centrifuge for 10 minutes at 300 RCF
11. Aspirate supernatant
12. Resuspend the cell pellet
13. Add 1.5ml of RNAlater
14. Transfer to a storage vial and freeze at -80°C.

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Collecting Viable Cells from CPT Tube #2

You'll need the following supplies:

Sterile PBS (Ca^{++}/ Mg^{++} free), this is used for washing and diluting.

90% FBS (Fetal Bovine Serum is heat inactivated, at 56°C for 30 minutes)/10% DMSO.

DMSO must be fresh and sterility maintained.

DMSO is stable at room temp for 6 months once opened.

1.After removal of the plasma. Remove the next layer called the "buffy coat", and place in a 15 ml conical tube. Add PBS slowly to bring the volume to 15 mls.

2.Mix the cells by gently inverting the tube 5 times.

3. Centrifuge for 15 minutes, room temperature at 300 RCF.

4. Aspirate as much of the supernatant as possible (using transfer pipette) without disturbing the cell pellet. Leaving a few mls of the supernatant (wash buffer) is ok.

5. Re-suspend the pellet by GENTLY vortexing or tapping with your finger.

6. Add PBS to bring the volume to 10 mls.

Once volume is 10 mls, count the number of cells. See Counting Cells using Hemocytometer slide. An automatic cell counter may be used (Coulter Counter)

7. Cap tube, mix cells by inverting 5 times.

8. Centrifuge 10 minutes, room temperature at 300 RCF.

9. Aspirate as much of the supernatant as possible (transfer pipette) without disturbing the cell pellet.

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Counting Cells using a Hemocytometer

- Remove 20ul from the cell suspension in # 6, add 20ul of 0.4% Trypan Blue.
- Load hemocytometer.
- Fill one chamber with 10ul of stained cell suspension. Let cells settle. If bubbles appear, clean the hemocytometer and start over.
- Assess for even cell distribution among the squares.
- Be sure to distinguish erythrocytes and lymphocytes.
- Count live cells in the four large corner squares. Include cells that touch either the top line or left vertical perimeter line of any square. Do not count those cells touching the bottom line or the right vertical perimeter line of any corner square.
- To calculate the # cells/ml use the following formula:
  - Viable cells/ml = (total # viable cells/squares counted) x 10^4 x dilution factor (this example the dilution factor = 2, 20ul cells, 20ul Trypan blue)
  - Viable cells = [(55+40+45+49)/4] x 10^4 x 2 = 94.5 x 10^4
  - Total viable cells = Viable cells/ml x volume of original cell suspension
    - Total viable cells = 94.5 x 10^4 x 10 ml = 94.5 x 10^5 = 9.45 x 10^6

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Collecting Viable Cells (cont'd)

10. Re-suspend the pellet of lymphocytes with a volume of cold 90% FBS/10%DMSO to make a cell concentration of 1.5-2x10^6 cells/ml. Re-suspend cells by tapping the tube gently with your finger until no clumps are visible. Do not vortex or pipette as this will damage the cells. Place the cell suspension on ice for 5 minutes to be sure they are cold.

11. Aliquot 1.0 ml of cell suspension into three barcode study labeled cryovials.

12. Quickly transfer tubes to -60°C to -90°C freezer until ready to ship.

13. Tubes can be shipped to the repository on dry ice.

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Intraop Bx

- Prior to Bx collection, prepare 6 cryovials (6 for recipients, 6 for donors) with RNALater and label them.
- Surgeon collects one core Bx at each time point in protocol (two time points per subject).
- Using sterile technique, the core Bx is divided into 3 segments and placed in cryovial, be sure the specimen is in the RNALater
- Freeze in -20°.

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Labeling

- Link to subject
- Print sample label page
- Collect blood/tissue
- Process Sample
- Label cryovials & storage tubes
- Documentation in database on sample label page

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Sample Labels

- DCC will send sites packages of pre-printed barcoded labels by subject class and visit.
- When you are ready to collect a sample, you will go into A2ALL-*Link* and associate the pre-printed labels you've received from the DCC with the subject and the study time point.

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Labels

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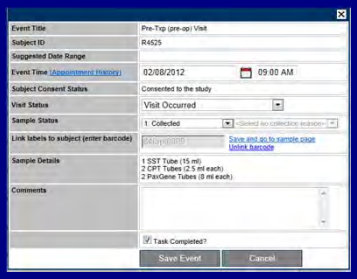
Subject "Consented to Study"



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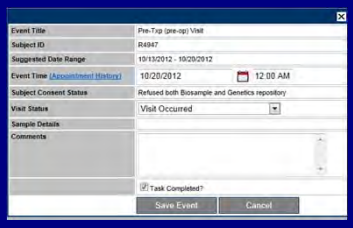
Subject "Refused both Repositories"



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Sample Label Page

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Labeling Blood Tubes

- Absolutely NO personal identifiers should be on tubes, i.e. S.S.N, names, D.O.B., etc.
- All tubes must have a Study ID# to be accepted.
- The Study ID# must begin with the site number, a hyphen, then a unique sample number.
- If labels are being used, apply lengthwise on tube over original Vacutainer label, do not wrap around.
- For all tubes-labels should not cover rubber top.

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Applying Labels to Adult Tubes

Correct

Incorrect

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Shipping Preparation

- YOU MUST SHIP ALL SAMPLES IN YOUR FREEZER MONTHLY (4th Monday of every month for NWU)
- The site will create a shipping manifest in A2ALL-*Link*. This manifest will be sent electronically to the repository and the DCC, on the day of shipment (see A2ALL-*Link* User Guide for instructions).
- The site will also print two shipping manifests one to be included in the shipment the other is a source document. If shipping more than one box, be sure to include a manifest in each box that corresponds to the bio-samples in each box.
- When the samples are received at the repositories, they will scan the bar codes and check them against the manifest. If there are any discrepancies between the manifest and the received samples, the DCC and the site will be informed.

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Shipping (cont'd)

- Print a manifest
- All shipments should be sent frozen
- The DCC will create a shipping calendar
- Pack the specimens according to the instructions included with the shipping kit
- Enter the weight of the dry ice as 4kg
- Put the appropriate stickers on the box
- Use the pre-printed FedEx airbill.
- Call Federal Express (1-800-GO-FEDEX) and FedEx will dispatch a courier to pick up the package

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A2ALL Study
Flow Sheet for Blood Sample Collection

Continued

- Use the enclosed Fed Ex shipping label.
- "Diagnostic Specimen Packed in Compliance with IATA Packing Instruction 650".
- Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339), and a courier will be dispatched to pick up the samples. Be sure to give Fed Ex the Zip Code of the PICKUP address, not that of the destination. NEVER PUT BLOOD KITS INTO FedEx DROP BOX!!!!

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Shipping Address (non-genetics)

Fisher BioServices
20301 Century Blvd.
Bldg. 6, Suite 400
Germantown, MD 20874

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Shipping Supplies (Non-Genetics)

- Each site is responsible for contacting the repository and requesting shipping supplies such as: storage boxes, shipping boxes, cartons, and shipping labels.
- Requests are made by e-mail only to: Bio-NIDDKrepository@thermofisher.com

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Shipping Supplies Genetics Only

- Supplies for genetic sample shipping can only be ordered on-line through the following web site:
- https://www.fisherbio.com/client/BSDWeb/NIDDK_A2ALL/login.asp

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MOO Overview

Manual of Operations

- Is a working document that should be referred to often for Standard Operating Procedures (SOPs).
- Located on A2ALL website, under Master Documents.
- Located on A2ALL-*Link* under Help Documents.

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MOO Overview

- Study Organization and History
- Regulatory Requirements
- Site Training and Activation
- Informed Consent Process
- Inclusion Criteria/ Potential Subject Cohorts
- Laboratory Test and Other Study Related Procedures
- Imaging Studies
- Hepatic Flow Measurements
- HRQOL & Donor Pain Survey Administration
- Annotated eCRFs
- Data Management
- A2ALL- *Link*
- Protocol Compliance
- Serious Adverse Event (SAE) Reporting

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SAE Definition

A serious adverse event (SAE) is any adverse experience that results in any of the following outcomes:

- death;
- life-threatening AE (i.e., one that places the subject, in the view of the investigator, at immediate risk of death from the AE as it occurs);
- persistent or significant disability/incapacity;
- required in-patient hospitalization, or prolonged hospitalization;
- congenital anomaly or birth defect.

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Serious Adverse Events

- Are only considered reportable if they occur as a result of a study procedure.
- Events, including deaths, that occur as a consequence of liver disease, liver transplant or liver donation are not considered reportable events for this study.
- While not considered an SAE, the study is concerned about donor deaths. Donor intraoperative or early post-op deaths should be reported to the DCC ASAP.

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Study-Related Procedures

- Venipuncture
  - Bleeding
  - Bruising
  - Infection at the site
  - Syncope
- Intraoperative Liver Biopsies
  - Bleeding (occasionally severe)
  - Death
- Pressure & Flow Measurements
  - Damage to vessel requiring surgical repair
- MRI
  - Claustrophobia
  - Anxiety
- CT scan
  - Reaction to the contrast dye

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Study-Related Procedures (cont.)

- HCV Study Protocol Biopsy
  - Bleeding
  - Death

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Documentation of SAE

- Date of onset
- Date of resolution
- Severity, relatedness, and expectedness
- Description and ICD-9 code for event
- Action taken- medications, procedures to treat SAE

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SAE Documentation Responsibility of PI

- We do not anticipate many SAEs in this study. We are only tracking events that are directly related to a study procedure.
- The Principal Investigator (PI) is responsible for reviewing the SAE being reported.
- The PI must assess whether the SAE is unexpected or expected.
- The PI must assess whether the SAE is unrelated or related to the study procedure.
- The PI must sign and date the review of the SAE.

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Reporting

Site Responsibilities:

- Report all serious adverse events to the DCC by filling out the SAE eCRF in the database (A2ALL-*Link*).
- All serious, unexpected, and related to study procedure events should be reported to your IRB within 7 working days of receipt of report.

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Reporting (cont'd)

- Report all serious, unrelated and expected events to your IRB at the renewal interval.
- Report all serious, unexpected and study related events that have occurred at other A2ALL sites to your IRB at the renewal interval.
- Sites submit Project Officer's letter summarizing the Data & Safety Monitoring Board (DSMB) report to IRB as study progress reports.

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Reporting – DCC Responsibilities

- The DCC reports all events that are serious, unexpected, and related to study procedures to all sites.
- Notifies the DSMB of all events at previously specified times during the course of the study
  - reports and tables

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Regulatory Documents

- DCC provides list of tabs in Manual of Operations (MOO) for binder.
- Study Protocol
  - All versions of the study protocol are to be kept in the binder (current on top)
  - Copies of Signed Principal Investigator Signature Pages
- CVs for investigators and all co-investigators
  - Include current appointments, positions and citations
  - Must include start and end dates for all appointments and positions
  - Signed and dated by Investigator (1st page of CV)
  - Updated bi-annually
- Medical license
  - Must be current with expiration date

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Regulatory Continued

- IRB approvals of the study to include protocol name, version and expiration date.
- IRB stamped copy of approved consent form
  - A copy is required
  - The copy must contain the IRB stamp of approval or IRB dates of approval (based on site's IRB requirements
- IRB Membership List
  - Must be current
  - If your IRB/ERC does not release its membership list, a DHHS multiple assurance number must be submitted on IRB/ERC letterhead.
  - If any investigator or co-investigator is a member of the IRB/ERC, a letter or IRB/ERC meeting minutes indicating that the person abstained from voting on the protocol MUST be submitted.

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Regulatory Continued

- Local Laboratory Information
  - Copy of the current CAP, and CLIA Certification along with certifications for the length of the study
  - Copy of current laboratory normal values for ALL protocol-mandated testing (dates for which the normal values are applicable must be noted)
  - Name of lab and date on document of lab normals
- Certification(HAZMAT) for Shipment of Biosamples

- The individual responsible for packaging, and shipment of serum/blood samples is required to have certification.

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Regulatory Continued

- Roles and Responsibility Log
  - All study personnel required to sign, initial and list their study responsibilities
  - Personnel must have start and stop dates of study responsibilities
- Certificate of Confidentiality (COC)
  - Obtained from NIH and maintained by the University of Michigan

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Regulatory Continued

- Documentation of Human Research Subject Participation Certification
  - National Institute of Health (NIH) website
  - Site/IRB
- Subject Screening Logs
- Monitoring Log – signature log
- Major Correspondence
  - IRB Correspondence
  - SAE, Data and Safety Monitoring Board (DSMB) letters from NIDDK Project Officers, and DSMB Reports
  - Protocol Amendments

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Screening Log

- For all subjects (prospective, gap and former), you will utilize an Excel spreadsheet listing all potential subjects and the result of your approach for consent.
- These logs are sent weekly (Mondays), to the DCC monitor for that site. The monitor reviews enrollment progress at each site.
- The weekly Enrollment Report is sent by the DCC to sites every week (Wednesdays)

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Screening Logs (cont)

- There are drop down answer boxes for the following:
  - Subject Type
  - Consent Status
  - Reason for Non-Enrollment
  - Donor or Recipient
  - Gender
  - Race
  - Ethnicity

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Screening Logs (cont)

- Subject Types:
  - Recipient
  - Donor
  - GAP
  - Former A2ALL
  - Long Term HRQOL Only (new centers only)
  - HCV Only
- Consented
  - Yes
  - No
- Reason for Non-Enrollment
  - Approached-refused
  - Approached-Dead
  - Approached-lost to follow-up
  - Approached-unresponsive
  - Not approached-language barrier
  - Not approached-staffing issues
  - Inclusion/Exclusion Criteria
  - Other (specify in comments)
- Donor and Recipient
  - Donor
  - Recipient

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Screening Logs (cont)

- Gender
  - Male
  - Female
- Race
  - American Indian or Alaskan Native
  - Asian (includes Indian, subcontinent)
  - Black or African American
  - Native Hawaiian or other Pacific Islander
  - White (includes Middle Eastern)
  - Multi-Racial, not specified
  - Unknown
- Ethnicity
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
  - Unknown

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Monitoring Plan

- On-site monitoring – DCC monitoring staff will visit your site annually. There will be ample advance notice.
  - Report from monitoring visit is sent to Principal Investigator (PI), copy to Study Coordinator(s), DSMB, and sponsor.
- Remote monitoring – via A2ALL-Link, reports are generated and sent on a regular basis.

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Monitoring Plan
Continued

- DSMB (Data and Safety Monitoring Board)
  - Appointed by NIDDK
  - Oversees the study's safety and progress
  - Purposes
    - Ensures monitoring activities are appropriate to the study
    - Monitoring is accomplished in a regular, timely and effective way
    - Recommendations that result from study monitoring are completed

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DATA AND SAFETY MONITORING PLAN
A2ALL CORE PROTOCOL

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1 Overview

Accepted principles of data and safety monitoring will be observed throughout the conduct of the A2ALL-2 Core Protocol. Serious Adverse Event reporting will follow the guidelines defined by the protocol. Since the study is largely observational the only research procedures that have the potential to generate an adverse event are venipuncture, intraoperative liver biopsy, intraoperative blood flow measurements, MRI and CT scans that are outside the standard of care at each institution.

Each transplant center principal investigator will be responsible for overseeing the A2ALL-2 Core Protocol at their institution, and the Data Coordinating Center (DCC) will be responsible for monitoring of the study. Monitoring responsibility will extend to determination of accurate and effective conduct of the protocol and to recommendations regarding closure of the study. The NIDDK has appointed an independent Data and Safety Monitoring Board (DSMB) that will review and approve the Core Protocol prior to any subject recruitment, and will continue to monitor the study's safety and progress through regular reports prepared by the DCC and periodic meetings, usually by teleconference, and in person as needed. For a listing for the Table of Contents for the DSMB Report, please refer to Appendix A.

Oversight of monitoring will be performed to ensure that: 1) monitoring activities are appropriate to the study, 2) monitoring is accomplished in a regular, timely and effective manner, and 3) recommendations that result from study monitoring are implemented in a timely fashion.

The Institutional Review Board (IRB) at each institution and the DCC will approve the study and all subsequent amendments and modifications. The IRB will also be provided information on study progress and serious adverse events on a regular basis.

Training of study coordinators and study monitoring activities will be conducted by the DCC to ensure understanding of the study protocol and procedures, maintenance of patient confidentiality and privacy, regulatory compliance,, and maximization of the reliability, accuracy, and timeliness of study data.

Prior to subject recruitment, the DCC will conduct a site initiation visit to assess each site's ability and readiness to conduct the protocol. Site personnel will be required to discuss and demonstrate their plans for approaching and consenting subjects, collecting data and samples, and performing data entry in a timely and accurate manner. When the site is approved to begin the study, the DCC will send the site an activation letter giving them permission to begin recruitment activities.

2 Risks to the Study Participant and Adequacy of Protection Against Risk

Subjects enrolled in the study will experience some study-related interventions or tests above and beyond those associated with the normal care delivered for the complicated medical and surgical procedures being studied. Additional time will be required both before and after the transplant for the gathering of medical and health-related quality of

life (HRQOL) information. Blood and liver tissue will be collected and stored for special tests that are not typically required for clinical care. Venipuncture has risks of pain and bruising at the puncture site. Intraoperative biopsy has the risk of bleeding. Portal and hepatic artery pressure and flow measurements also have the risk of bleeding and/or damage to the vessel(s). All research procedures will be carried out by qualified personnel who are experienced in performing the tasks.

Pain and bruising related to venipuncture will be minimized by having the sites utilize trained venipuncture technicians, and issues that arise will be addressed immediately by local study personnel on site. Intraoperative bleeding and/or vessel damage related to intraoperative biopsy and/or pressure and flow measurements will be minimized by utilizing careful, standardized technique performed by highly skilled liver transplant surgeons. Routine surgical interventions will be used by highly skilled liver transplant surgeons to address these issues in the event that they arise.

The study subject interviews and the HRQOL instruments do not involve any known physical risks. Individuals may experience psychological discomfort in answering repeated, longitudinal assessment questions related to their emotional well-being, health concerns and worries, relationship problems, or financial hardships. With respect to potential discomfort developing during interviewing, we note that the interviewers will be trained by the investigators to be sensitive to participant discomfort and concerns. Steps to minimize risk and address any psychological discomfort are addressed below.

> Psychological discomfort during study procedures (i.e., during study assessments). Awareness of participant's psychological distress and well-being will be a central focus of the interviewers' training. If a participant finds the research procedures to be upsetting or unpleasant, he/she will be offered the option to discontinue the interview or withdraw entirely from the study. Study personnel will refer participants to an appropriate clinical provider for evaluation and/or treatment in the unlikely event that an interviewer judges that (a) the subject immediately requires such care for psychological distress, or (b) the subject inquires about receiving such care. The criterion for establishing that a participant immediately requires care is the expression by the subject of thoughts of or a stated intention to harm oneself or others. During the HRQOL assessment, interviewers will be alert for any statements volunteered by the participant regarding thoughts or intent for harm or for the participant's affirmative response to the PRIME-MD items that refer to thoughts or intent of harming oneself or others. In this situation, confidentiality would be broken in order to protect the participant. The participant will be made aware of this contingency in the informed consent form. If this circumstance arises, the interviewer will initially consult the specific center study coordinator to arrange for an evaluation at the respective institution, or at a local facility in the geographical area where the participant resides if he/she lives a long distance from the living donor transplant program and prefers a local referral. This approach meets IRB guidelines, and these procedures have successfully facilitated such local and long-distance

arrangements in our past studies. These procedures have had to be invoked extremely rarely in our and our investigators' experience.

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3 Data Management

All study data will be entered into the *A2ALL-Link* electronic data entry system by study Coordinators at each study site. This data will be encrypted during transmission to the DCC and will be stored on a secure server. Access to the server and *A2ALL-Link* system is strictly limited and requires a unique username and password combination. The servers are backed up daily and physically stored in a locked facility.

All analysis of data will utilize de-identified (coded) data sets to avoid compromise of protected health information.

3.1 Quality Control and Database Management

The first steps in ensuring protocol compliance are good protocol design and careful orientation of study personnel. Following final agreement on protocols, and prior to study initiation at any of the transplant centers, the DCC will organize a Training and Certification session for transplant center study coordinators/data entry personnel.

The *A2ALL-Link* electronic data entry system will have built-in two-stage point of entry data checks as part of study data quality assurance. Protocol compliance will be assessed by monitoring the submission of data at required intervals. Data inconsistencies and discrepancy reports will be reviewed by the Clinical Monitors so that necessary queries can be generated and sent to the transplant center study sites for verification and resolution.

Periodic requests may be generated for the submission of random source documents to assess the quality and completeness of data acquisition and data entry at each site. In addition, the Clinical Monitors or Project Manager will visit each site at least annually to review source documents, monitor regulatory compliance, and assess protocol adherence.

In addition to source document verification, the Clinical Monitors and Project Manager will produce reports from the *A2ALL-Link* system identify inconsistencies in submitted data, particularly for data elements that are assessed serially, even if data do not fall outside of built-in validation limits.

Studies of intra-subject and inter-subject data variability by transplant center as well as intra-transplant center and inter-transplant center data variability will be used to further ascertain random or systematic data quality issues.

Site-specific "report cards" will be produced for periodic distribution to the study sites and review by the DCC, the Project Executive Committee, and the Steering Committee.

3.2 Data Security/Data Transfer

All collected through the *A2ALL-Link* system are initially stored in a Microsoft SQL Server database, implemented with industry-standard practices to protect the security and integrity of these data. Audit trails are maintained for all *A2ALL-Link* activity and all changes to any data element in the system.

All *A2ALL-Link* database servers, web servers, firewalls, etc., are configured and maintained according to industry best practice guidelines for backup, security, continuity of operations, and protection of protected health information. They are housed within a security boundary, with a comprehensive security plan certified by the US Health Resources and Services Administration (HRSA/HHS).

- At a minimum, FIPS 140-2 Level 1 Cryptographic Integrity
- HIPAA–compliant collection and storage of protected health information
- Data structures are modeled on ISO standards
    - 4217 Currency Codes
    - 3166 Culture/Country Identification
- SANS Security Essentials
- World Wide Web Consortium (W3C) Specifications
    - HTML 4.0
    - XHTML 1.0
    - JavaScript 1.2+
    - CSS 2.0
- All transmissions between Internet users and *A2ALL-Link* are encrypted using a 128-bit encryption algorithm.
- Logins for user accounts are managed using industry standard security practices, storing n HMAC-SHA1 hash of user passwords; credentials are not known to the DCC.
- The web server is the only Internet-facing computer running *A2ALL-Link* software.
- All database queries accessible from the web server are internally developed stored procedures to prevent SQL injection and other similar problems; all access is based on least privilege.
- All computers that house secure website software and data reside in a locked, monitored, climate-controlled room.

4 Clinical Monitoring Plan Overview

4.1 Onsite Monitoring

1. DCC staff will travel to each active study site on an annual basis to perform on-site study monitoring.
2. Site study coordinators and Principal Investigators will be contacted with proposed dates of monitoring visit at least six weeks in advance.

3. Sites should plan for an approximately three day monitoring visit, allowing at least one hour near the conclusion of the visit for the Principal Investigator to meet with the monitor(s) to cover any issues that may have arisen during the visit.
4. A letter confirming the visit will be sent via email to the study coordinator. The Principal Investigator will be mailed an original. The confirmation letter should be sent to the site at least six weeks prior to the visit date.
5. The confirmation letter will outline the visit activities and note any local resources that the monitors will need to accomplish a successful visit.
6. The confirmation letter will include a list of subjects to be monitored during the visit. The subject list may contain 20 to 30 subjects.
7. Four weeks prior to the visit, site study coordinators will be provided, via e-mail, pre-monitoring queries for the subjects chosen for the visit. The site study coordinators will resolve the queries and e-mail the resolutions to the monitors no less than one week prior to the visit.
8. The study coordinators are responsible for arranging for all necessary source documents to be accessible during the visit.
9. Once the monitors arrive at the site, 50%-75% of the preselected subjects will be chosen from the list at random for a full review. Informed consent documentation will be monitored for 100% of the subjects chosen for review.
10. Monitors will review the chosen subjects for accuracy and completeness of data submitted versus available source documents.
11. Monitors will focus on unresolved queries and discrepancies as well as those discovered during the visit.
12. An attempt to locate missing items should be done before the visit end. If this is not possible, a follow-up call to the site may be necessary.
13. Monitors will review the Regulatory Binder(s) for accuracy, currency, and completeness.
14. Monitors will sign a monitor log before the visit is complete.
15. Unresolved monitoring queries remaining at the conclusion of the monitoring visit should be resolved (including provision of source documentation, as necessary) by the site study coordinators and communicated to the DCC within four weeks of the monitoring visit.
16. A written report of the monitoring visit will be generated by the Clinical Monitor(s) no more than four weeks after visit completion.
17. The monitoring report will contain detailed information about the visit, what was done at the visit, and steps taken to resolve any identified issues. Whenever possible, queries and issues identified or reviewed during the site visit should resolve prior to the visit's conclusion.
18. Once the monitoring report has been reviewed by the DCC, it will be sent to the Principal Investigator and the study coordinator. The report is to be retained in the Regulatory Binder(s).
19. Monitoring reports will be shared with the Project Executive Committee, the NIDDK Project Scientist, and the DSMB.
20. If a site demonstrates persistent deficiencies in one or more areas, the DCC will note this in the monitoring report. The DCC may request that the site provide an

action plan for remediation, and/or institute an enhanced intensity or frequency of monitoring.

4.2 Remote Monitoring Plan

1. Between site visits, remote monitoring will be conducted by the DCC. This monitoring includes: random monitoring of source documents, generation of queries arising from data quality and sample collection reports, monitoring of discrepancies automatically generated by the database. A2ALL Clinical Monitor(s) will review randomly chosen subjects (10%) from each site during the 3-6 months following each site visit. Sites will provide de-identified source documents as requested by the clinical monitoring staff.
2. Queries generated by the remote monitoring process will be sent directly to the site study coordinator for resolution. As with other queries, the site will have generally been given four weeks to address all queries.
3. Subjects who are remotely monitored will not be included in the annual monitoring visit.

5 Serious Adverse Events

For this observational study, the majority of the procedures and interventions being studied are part of the standard clinical care that would be delivered to these patients, whether or not they were subjects in the study. Deviations from the normal clinical course will be tracked as complications by the study but will not be considered Adverse Events or Serious Adverse Events, unless they are related to interventions specifically called for by the study protocol and specifically not considered part of the standard clinical care of the subject as a patient at the site. Each center will review the list of study procedures and identify specific study interventions that meet these criteria at their institution, and these will be considered research procedures or interventions. Complications that result from such protocol-related procedures or interventions will be reported and tracked as Adverse Events or Serious Adverse Events, as appropriate.

Serious Adverse Events related to the protocol mandated procedures will be reported by the sites to the DCC. The following are considered study procedures in the Core Protocol:

- Phlebotomy
- HRQOL surveys
- MRI/CT scan at 90 days post-donation for donors (site-dependent)
- Intraoperative donor and recipient liver biopsy
- Intraoperative pressure and flow measurements

For an event to be considered as a Serious Adverse Event, one or more of the following must apply:

- Death
- Life threatening
- Persistent or significant disability/incapacity
- Required in-patient hospitalization or prolonged hospitalization
- Congenital anomaly or birth defect
- Important medical events requiring medical or surgical intervention to prevent one of the outcomes listed above

Serious Adverse Event reporting begins with the first study procedure and ends 30 days after last study procedure. Serious Adverse Events must be reported to the DCC within 24 hours of the site's awareness of the occurrence. The site should complete the Serious Adverse Event report form in A2ALL-Link within this time frame. Once the form is saved, notification will be sent to the DCC and NIDDK. The DCC will report Serious Adverse Events to the DSMB and IRBs on a periodic basis. Deaths arising from a study procedure will be reported to the DSMB and IRBs within 48 hours of the DCC becoming aware of the event.

6 Appendix A: Table of Contents for Planned A2ALL-2 Core Protocol DSMB Reports

Subject Enrollment
- Cumulative Enrollment
- Enrollment by Site
- Transplant and Donation Activity

Characteristics of Recipients

Characteristics of Donors

Sample Collection
- Cumulative Sample Collection
- Expected vs. Completed Sample Collection by Site

HRQOL Survey Completion
- Cumulative Survey Completion
- Expected vs. Completed Survey Completion by Site

Data Quality
- Compliance with Completion of Study Visits and Associated CRFs
- Compliance with Study Procedures and Associated CRFs
- Data Discrepancy Reports

Site Report Cards (summary reporting of protocol compliance and data completeness, accuracy, and timeliness)

Protocol Deviation and Violation Report

Serious Adverse Event Report

Clinical Monitoring Reports

A2ALL
Adult to Adult Living Donor Liver Transplantation Cohort Study

Remote Monitoring Plan

1. A2ALL Study monitors will review randomly chosen subjects (10%) from three sites based on the following schedule:

   Should be based on the monitoring schedule and in conjunction with the queries generated through the data base by the analysts. No site should be randomly monitored if the site visit is to occur during that time frame.

   Between site visits, remote monitoring will occur at the DCC. This monitoring includes: random monitoring of source documents, generation of queries arising from data quality reports, monitoring of discrepancies automatically generated by the database.

   The DCC analysts will need to run the discrepancy reports in order to determine which subjects to be chosen for monitoring. The most important discrepancies to be utilized: delinquent post transplant assessment forms, hospitalization, complication, rejection, HCV and HCC.

2. Only select forms will be monitored for discrepancies and inconsistencies. A2ALL Cohort for Recipients, RCP condition at donor Eval, RCP @ TXP, Intraop Form, 1mth, 3mth and 1 year, Hosp, Comps and Rejection, HCC and HCV; for donors Donor Eval, Donation Surgery, 1 mth, 3 mths, 1 year, Hosp., Comps.,

3. Study monitors will focus on subjects which demonstrate large number of discrepancies based on the generated reports from the analysts.

4. Queries generated through the remote monitoring process will be sent directly to the site study coordinator for resolution. As with other queries, the site will have four weeks to address all queries.

5. The subjects randomly monitored will not be included in the annual monitoring visit.

Documentation of Consent Process

A2ALL: Adult-to Adult Living Donor Liver Transplantation Cohort Study

Patient Medical Record number:_____

I discussed the risks, benefits, and alternatives with the patient and reviewed the consent form on <insert date>. I answered all questions to his/her satisfaction. The patient agreed to participate in the research study and signed the consent form prior to completing any research procedures. A copy of the consent form was given to the subject. The subject was enrolled in the A2ALL Cohort study and assigned subject number XXXXXX.

_____ _____

Signature of Person Obtaining Consent Date

Additional notes, if needed:

SUBJECT ID#: **D**_____

NAME: _____

DONATION DATE: __/__/20___

A2ALL
Adult to Adult Living Donor Liver Transplantation Cohort Study

A2ALL CORE PROTOCOL DONOR INTRAOPERATIVE DATA

Surgery Information

B-1 Donor Height: _____ inches/cm

B-2 Donor Weight: _____ lbs/kg

C-1 Was the donation procedure aborted before completion? (if no, go to question C-5)
_____ Yes
_____ No

C-1-1 If yes to procedure abortion, why was the procedure aborted? (Check all that apply)
_____ Quality of donor liver
_____ Insufficient liver mass
_____ Technical difficulties in the donor
_____ Donor instability
_____ Unexpected medical findings in the recipient
_____ Recipient instability
_____ Recipient death on table
_____ Other, specify _____

C-2 Did the donor receive general anesthesia?
_____ Yes
_____ No

C-3 Was the liver parenchyma divided?
_____ Yes
_____ No

C-4 Was the lobe removed from the donor?
_____ Yes
_____ No

C-5 Was the donation procedure performed laparoscopically?
_____ Yes
_____ No

C-6 Was the donated lobe transplanted?
_____ Yes
_____ No

SUBJECT ID#: **D_____**

NAME: _____

DONATION DATE: __/__/20___

C-7 Was the donated graft transplanted into the originally-intended recipient?
_____ Yes
_____ No

C-7-1 If no to graft transplantation, why wasn't the resected graft transplanted into the recipient? (Check all that apply)
____ Quality of donor liver
____ Insufficient liver mass
____ Recipient instability
____ Unexpected medical findings in the recipient
____ Recipient death on table
____ Other, specify _____

C-8 Was a pre-operative or intraoperative biopsy (biopsy other than biopsy performed to collect tissue for the study) of the donor liver performed?
_____ Yes
_____ No

C-8-1 If yes, what was the percentage of macrovesiclar fat noted on the biopsy report?
_____ %
_____ Not noted

C-8-2 If yes, what was the percentage of microvesiclar fat noted on the biopsy report?
_____ %
_____ Not noted

C-8-3 Other findings noted?
_____ Yes
_____ No

C-8-4 If yes to other findings, specify _____

C-9 Lobe Recovered:
_____ Right Lobe
_____ Left Lobe
_____ Left Lateral Segment

C-10 Was the middle hepatic vein included?
_____ Yes
_____ No

C-11 What was the weight of the resected lobe (graft weight)?
_____ gm

C-12 Was auto-transfusion used?
_____ Yes
_____ No

C-12-1 If yes, total amount transfused: _____ cc

SUBJECT ID#: **D_____**

NAME: _____

DONATION DATE: __/__/20___

C-13 Was banked blood given to the subject during donation surgery?
_____ Yes
_____ No

C-13-1 If yes, number of predonated autologous units: _____
C-13-2 If yes, number of non-autologous units: _____

C-14 Did the subject experience any episode(s) of systolic BP<100 mmHg during the surgery?
_____ Yes
_____ No

C-14-1 If yes, indicate total duration of the episode(s). Add together if more than one episode.
_____ minutes

C-15 Did the subject experience systolic BP<80 mmHg for 5 or more minutes during the surgery?
_____ Yes
_____ No

C-16 Did any intraoperative injuries occur?
_____ Yes
_____ No

C-16-1 If yes, which structure(s) were injured (check all that apply)
_____ Bile Duct
_____ Hepatic Artery
_____ Portal Vein
_____ Other, specify: _____

C-17 Cross clamp time (24-hour clock time): ___:___

SUBJECT ID#: **D**_____

NAME: _____

DONATION DATE: __/__/20___

Anatomy

D-1 Select the figure below that indicates the donor's biliary anatomy

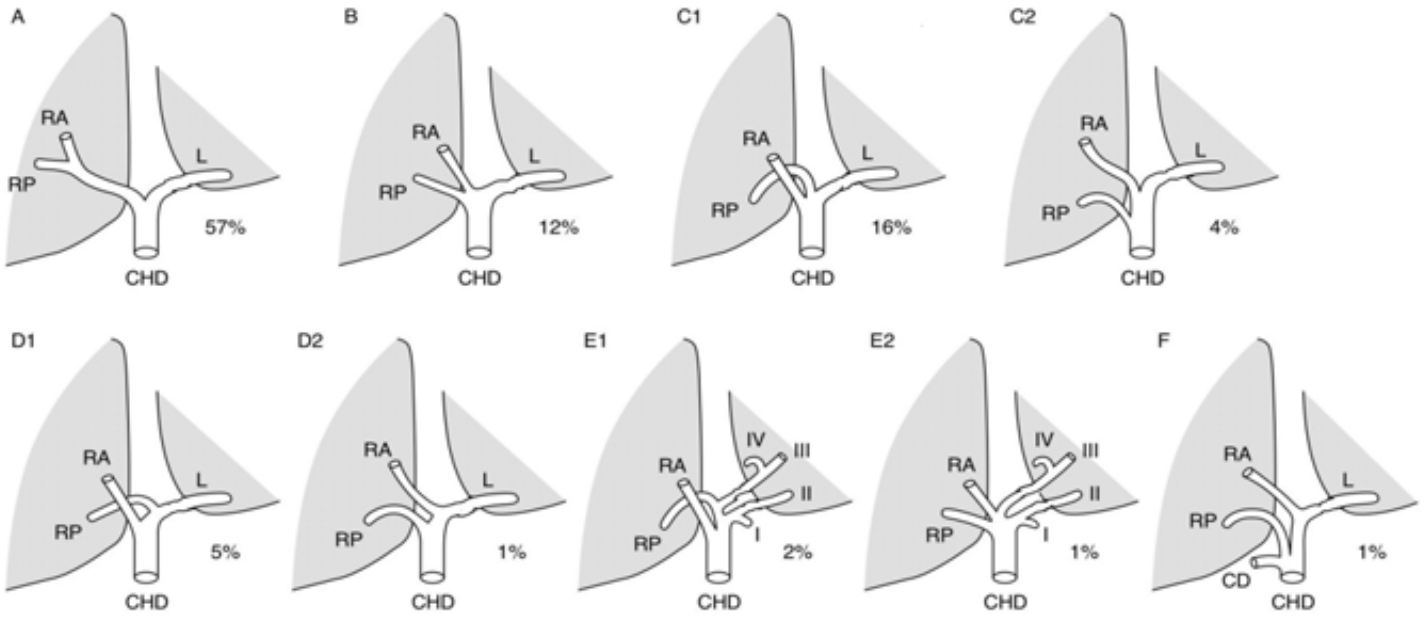


Fig. 10 Variations and anomalies of the biliary tree in relation to split and living related liver transplantation. CHD, common hepatic duct; RA, right anterior hepatic duct; RP, right posterior hepatic duct; L, left hepatic duct; CD, cystic duct

_____ A
_____ B
_____ C1
_____ C2
_____ D1
_____ D2
_____ E1
_____ E2
_____ F
_____Other

SUBJECT ID#: **D**_____

NAME: _____

DONATION DATE: __/__/20___

D-2 Select the figure below that indicates the donor's hepatic venous anatomy

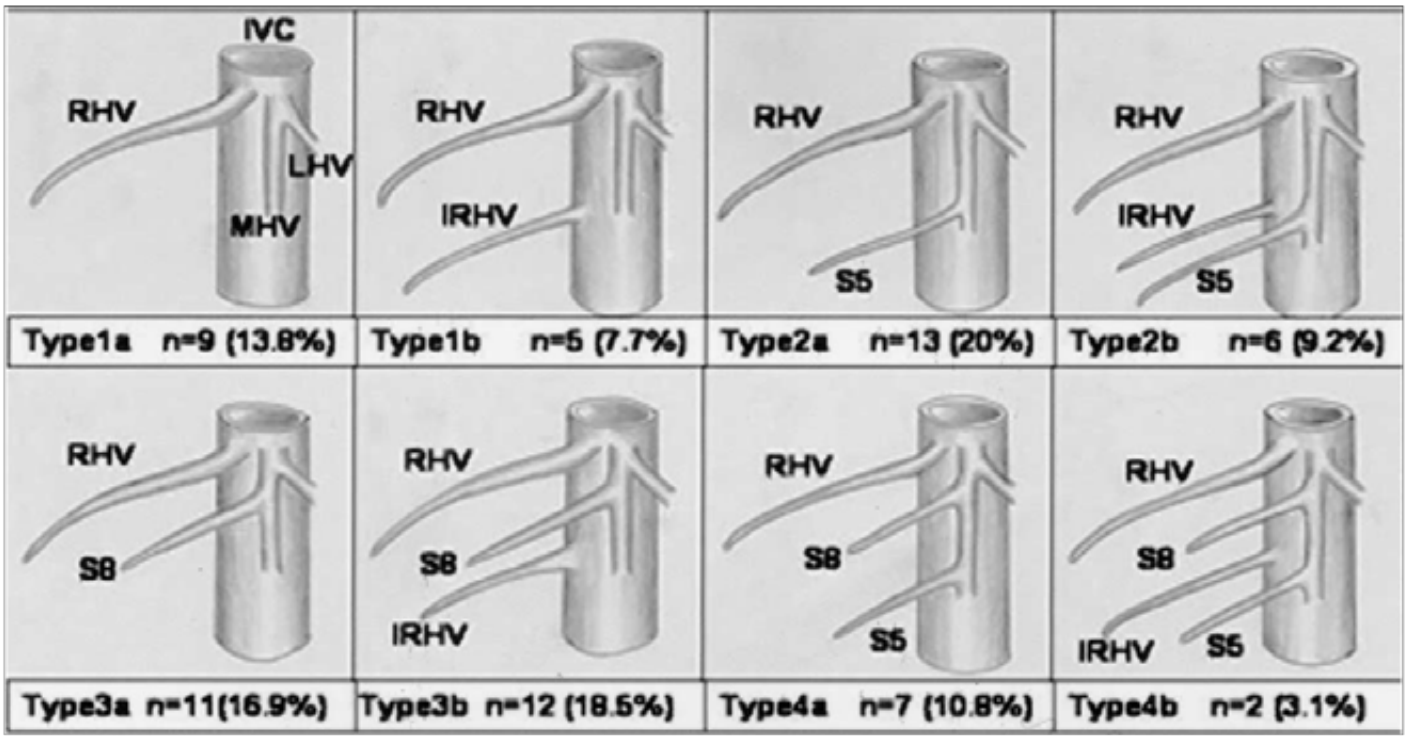


Figure 4. Classification and incidence of the right liver hepatic venous anatomy. IRHV; inferior right hepatic vein; IVC, inferior vena cava; LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein.

_____ Type 1a
_____ Type 1b
_____ Type 2a
_____ Type 2b
_____ Type 3a
_____ Type 3b
_____ Type 4a
_____ Type 4b

D-3 Right lobe graft hepatic venous anatomy: Select vein >5mm preserved for anastomosis:
_____ Right hepatic vein including all segments
_____ Right hepatic vein with separate segment 8
_____ Right hepatic vein with segment 5 and 8 separate
_____ Right hepatic vein with segment 6 separate
_____ Other, Specify: _____

D-4 Left lobe graft hepatic venous anatomy:
_____ Single orifice for segments 2, 3, 4
_____ Single orifice for segments 2 and 3 with separate orifice for segment 4
_____ Single orifice for segments 3 and 4 with separate orifice for segment 2
_____ Other, specify: _____

D-5 Left lateral segment graft hepatic venous anatomy:

SUBJECT ID#: **D**_____

NAME: _____

DONATION DATE: __/__/20___

_____ Single orifice for segments 2 and 3
_____ Separate orifices for segment 2 and segment 3
_____ Other, specify: _____

D-6 Select the figure below that indicates the donor's portal venous anatomy

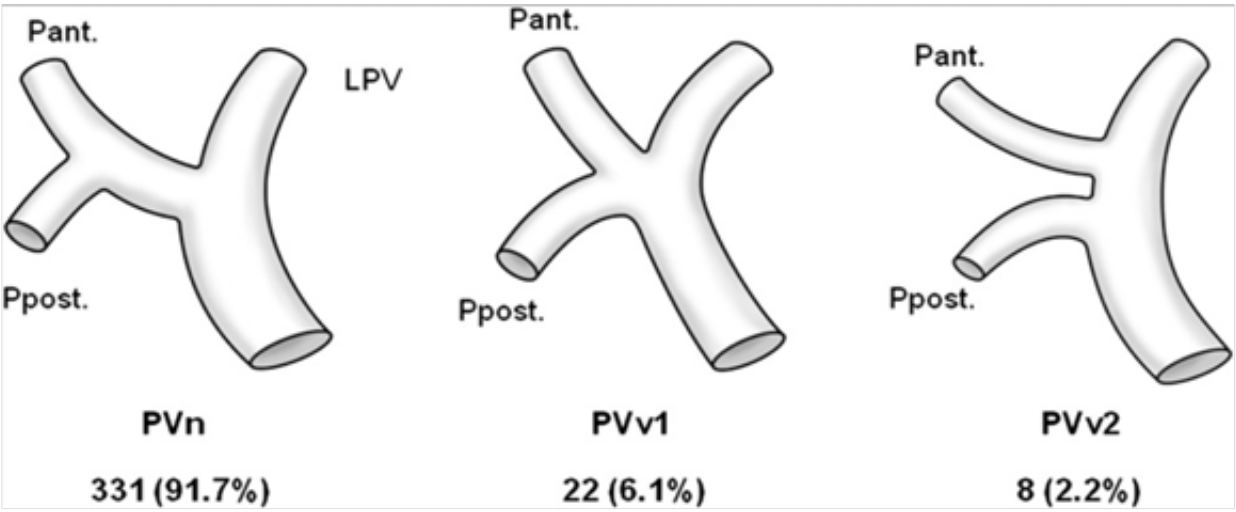


Fig 1. Classification of PV anatomy in 361 donors.

_____ PVn
_____ PVv1
_____ PVv2
_____ Other

SUBJECT ID#: **D**_____

NAME: _____

DONATION DATE: __/__/20___

D-7 Select the figure below that indicates the donor's hepatic arterial anatomy

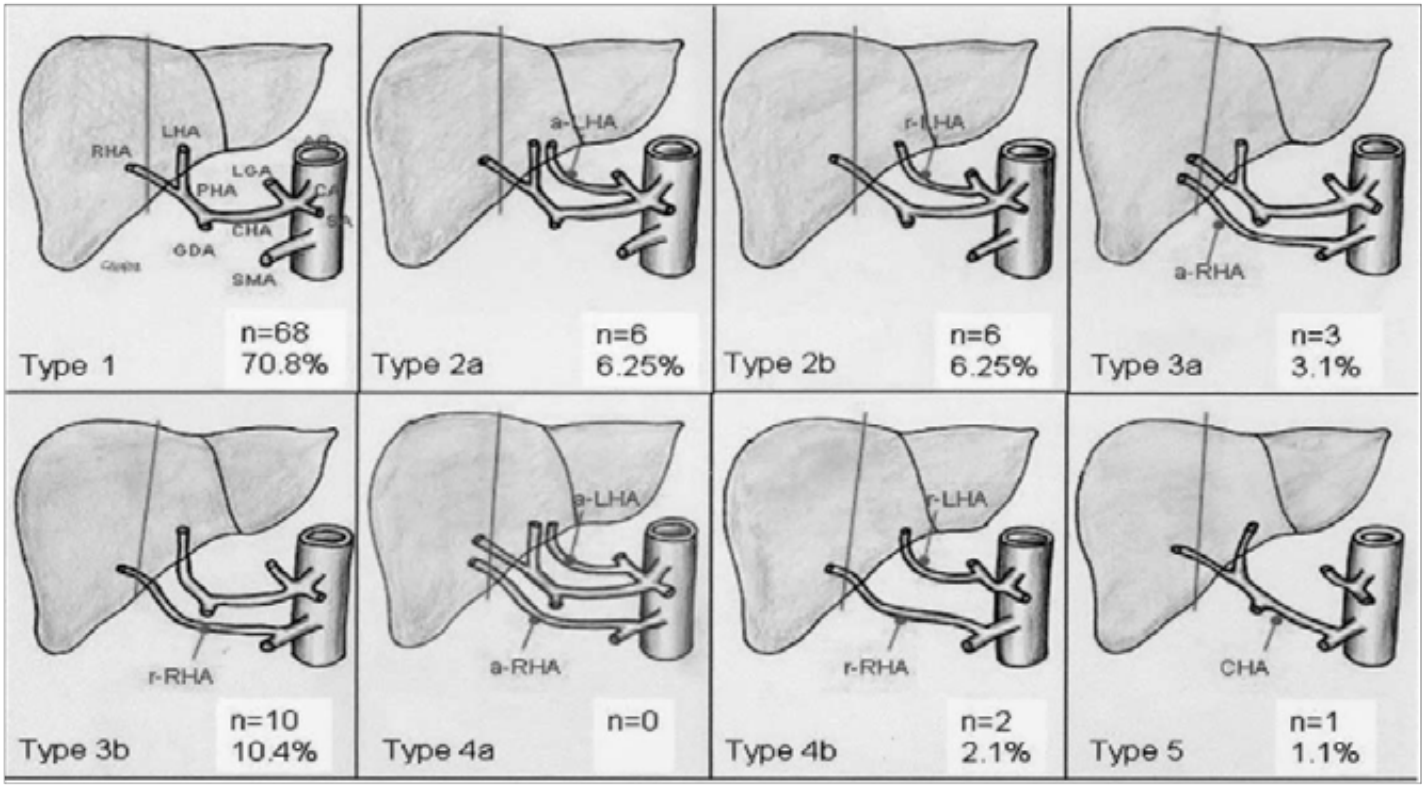


Figure 2. Classification and incidence of the hepatic artery anatomy. AO, aorta; CA, celiac axis; CHA, common hepatic artery; GDA, gastroduodenal artery; LGA, left gastric artery; LHA, left hepatic artery; PHA, proper hepatic artery; RHA, right hepatic artery; SA, splenic artery; SMA, superior mesenteric artery.

_____ Type 1
_____ Type 2a
_____ Type 2b
_____ Type 3a
_____ Type 3b
_____ Type 4a
_____ Type 4b
_____ Type 5
_____ Other

D-8 Does the arterial supply to segment 4 arise from the left hepatic artery or the right hepatic artery?

_____ Left hepatic artery
_____ Right hepatic artery

Surgeon Signature: _____ Date: _____

SUBJECT ID#: **R**_____
NAME: _____
TRANSPLANT DATE: __/__/20___

A2ALL CORE PROTOCOL RECIPIENT INTRAOPERATIVE DATA

DONOR INFORMATION

C-1 Donor Height: _____ inches/cm

C-2 Donor Weight: _____ lbs/kg

Surgery Information

C-3 Was the transplant procedure aborted before completion?
____ Yes
____ No

C-3-1 If yes to procedure abortion, why was the procedure aborted? (Check all that apply)
____ Quality of donor liver
____ Insufficient liver mass
____ Technical difficulties in the donor
____ Donor instability
____ Unexpected medical findings in the recipient
____ Recipient instability
____ Recipient death on table
____ Other, specify: _____

C-4 Graft type:
____ Right Lobe
____ Left Lobe
____ Left Lateral Segment

C-5 What was the weight of the graft? _____ gm

C-6 Cross clamp time (24-hour clock time): ___:___

C-7 Out of ice time (24-hour clock time): _____:___

C-8 Portal reperfusion time (24-hour clock time): _____:___

C-9 Arterial reperfusion time (24-hour clock time): _____:___

C-10 Were any of the following medications used during the transplant procedure (intraoperatively or immediately post-operatively): Octreotide, Propanolol, or Vasopressin?
____ Yes
____ No

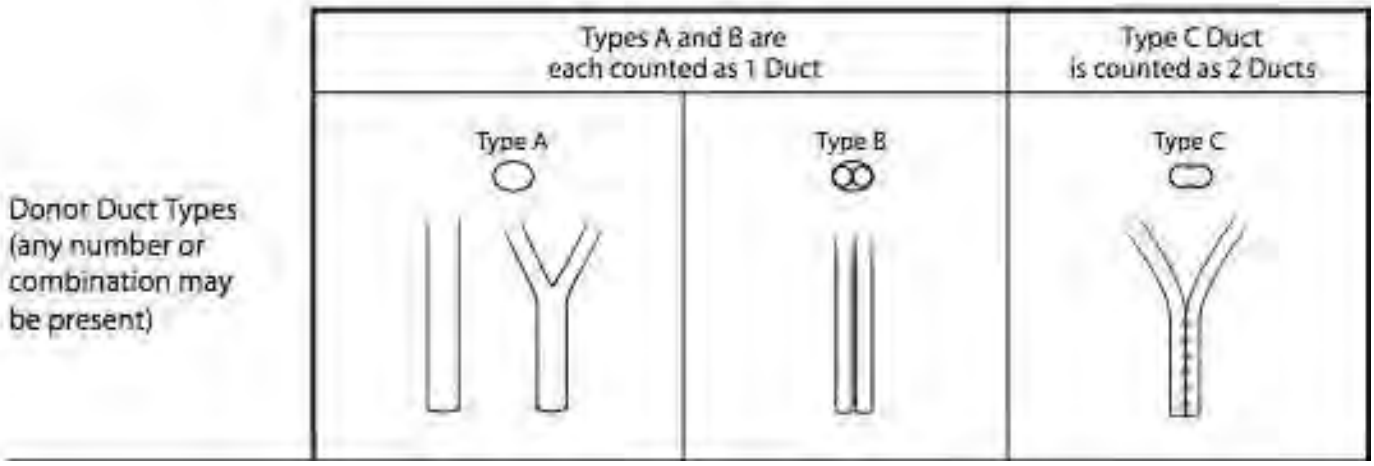
SUBJECT ID#: **R_____**
NAME: _____
TRANSPLANT DATE: __/__/20___

C-10-1 If yes, which medications were used? (check all that apply)
____ Octreotide
____ Propanolol
____ Vasopressin

Operative Reconstructive Details

Biliary Reconstruction

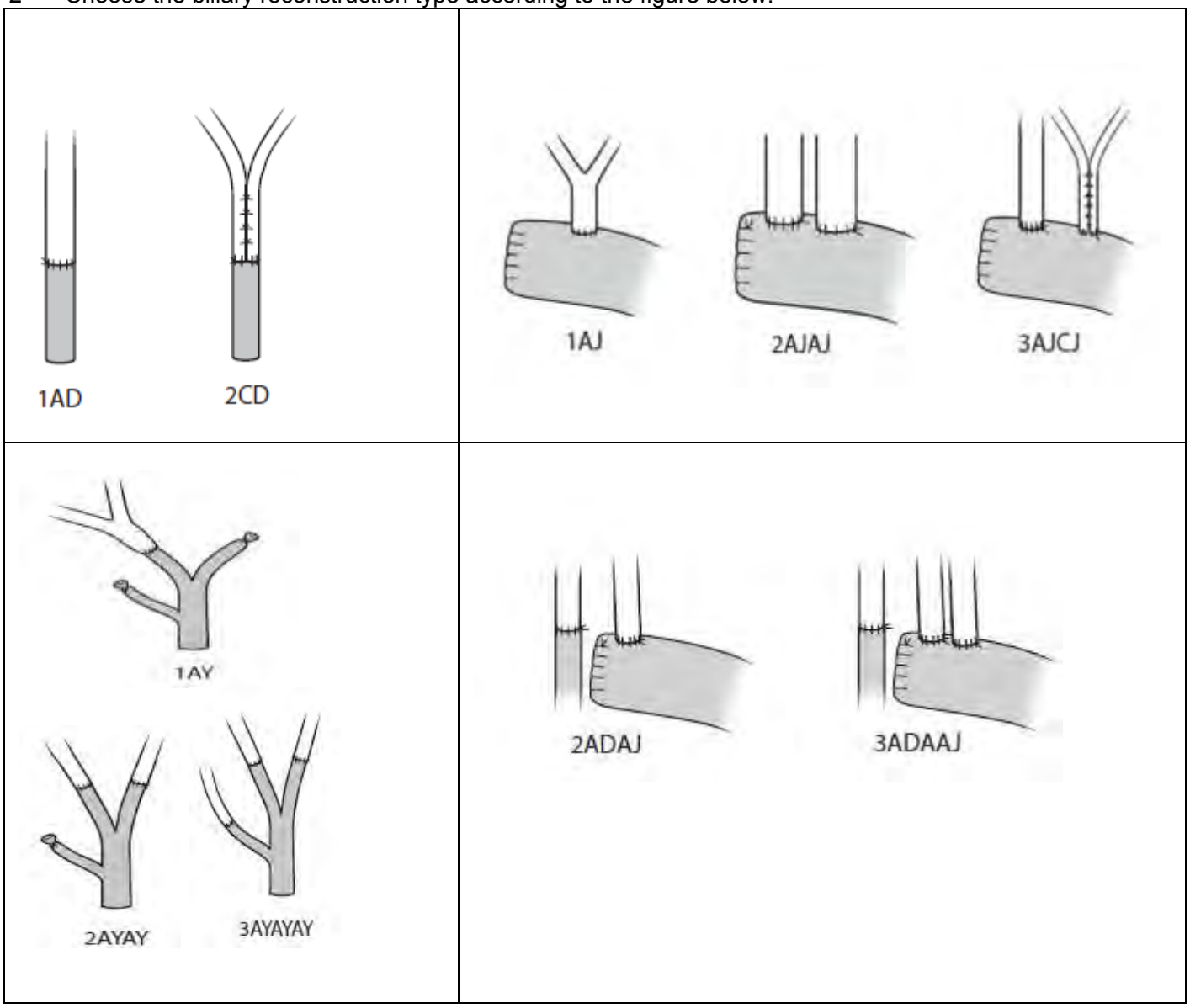
D-1 Choose the donor bile duct management from the choices on the figure below:



____Type A
____Type B
____Type C
____More than 2 ducts

SUBJECT ID#: **R**_____
NAME: _____
TRANSPLANT DATE: __/__/20___

D-2 Choose the biliary reconstruction type according to the figure below:



_____ 1AD
_____ 2CD
_____ 1AJ
_____ 2AJAJ
_____ 3AJCJ
_____1 AY
_____2 AYAY
_____3 AYAYAY
_____2 ADAJ
_____3 ADAAJ

SUBJECT ID#: **R_____**
NAME: _____
TRANSPLANT DATE: __/__/20___

D-3 Was an accessory duct oversewn?
____ Yes
____ No

D-4 Was a stent used in the reconstruction?
____ Yes
____ No

Hepatic Venous Reconstruction

D-5 Was there back table ligation of any segmental veins?
____ Yes
____ No

D-6 Was the middle hepatic vein included?
____ Yes
____ No

D-7 Right lobe graft hepatic venous reconstruction (*only answered if Right lobe graft)*:
____ Right vein includes all segments and anastomosed to vena cava
____ Right vein anastomosed to vena cava and V6 anastomosed separately
____ Right vein anastomosed to vena cava plus V8 anastomosed to vena cava without interposition
____ Right vein anastomosed to vena cava plus V8 anastomosed to vena cava with interposition
____ Right vein anastomosed to vena cava plus V5 anastomosed to vena cava with interposition
____ Right vein anastomosed to vena cava plus V5 and V8 anastomosed to vena cava with interposition
____ V5, V6, V7, V8 anastomosed separately with interposition for V5 and V8

D-7-1 If yes to interposition graft, indicate the type of conduit used:
____ Cryopreserved vessel
____ Fresh homologous vessel
____ Fresh autologous vessel
____ PTFE conduit

D-8 Left lobe graft hepatic venous reconstruction *(only answered if Left lobe graft):*
_____ Common orifice left and middle hepatic vein to recipient vena cava
_____ Common orifice left and middle hepatic vein to recipient common orifice of left and middle hepatic vein
_____ Separate implantation of left hepatic vein and middle hepatic vein to recipient vena cava

D-9 Left lateral segment graft hepatic venous reconstruction (*only answered if Left lateral segment graft):*
_____ Left hepatic vein to recipient vena cava
_____ Left hepatic vein to recipient common orifice of left and middle hepatic vein

SUBJECT ID#: **R_____**
NAME: _____
TRANSPLANT DATE: __/__/20___

Portal Venous Reconstruction (All Grafts)

D-10 Portal venous reconstruction:
_____ End-to-End
_____ Interposition graft

D-10-1 If yes to portal vein interposition graft, type of conduit used:
____ Cryopreserved vessel
____ Fresh homologous vessel
____ Fresh autologous vessel
____ PTFE conduit

Hepatic Artery Reconstruction (All Grafts)

D-11 Number of hepatic arteries reconstructed:
_____ 1
_____ 2
_____ More than 2

Portal Vein Flow Modulation Information:

E-1 Was intraoperative portal vein modulation done?
_____ Yes
_____ No

(if E-1 is Yes, then each of the rest of the questions in section E must be answered).

E-2 Was a splenectomy performed?
_____ Yes – before reperfusion
_____ Yes – after reperfusion
_____ No

E-2-1 If yes, why was the modulation done? (check all that apply)
____ Graft size
____ Portal pressure
____ Portal gradient
____ Portal flow
____ Arterial flow

E-3 Was a splenic artery ligation performed?
_____ Yes – before reperfusion
_____ Yes – after reperfusion
_____ No

E-3-1 If yes, why was the modulation done? (check all that apply)
____ Graft size
____ Portal pressure
____ Portal gradient
____ Portal flow
____ Arterial flow

SUBJECT ID#: **R**_____
NAME: _____
TRANSPLANT DATE: __/__/20___

E-4 Was a portocaval shunt done?
_____ Yes – before reperfusion
_____ Yes – after reperfusion
_____ No

E-4-1 Shunt size: _____ mm

E-4-2 Shunt material:
____ Cryopreserved vessel
____ Native portal vein
____ Fresh homologous vessel
____ Fresh autologous vessel
____ PTFE conduit

E-4-3 If yes, why was the modulation done? (check all that apply)
____ Graft size
____ Portal pressure
____ Portal gradient
____ Portal flow
____ Arterial flow

E-5 Was a collateral vein ligated as a portal vein flow modulation?
_____ Yes – before reperfusion
_____ Yes – after reperfusion
_____ No

E-5-1 If yes, why was the modulation done? (check all that apply)
____ Graft size
____ Portal pressure
____ Portal gradient
____ Portal flow
____ Arterial flow

SUBJECT ID#: **R_____**
NAME: _____
TRANSPLANT DATE: __/__/20___

PRESSURE AND FLOW MEASUREMENTS:

Document the flows and pressures on the next page. Measurements should be performed in the native liver prior to its removal and then repeated after graft reperfusion. Flow measurements should be repeated after any portal flow modulation. Print the record of each measurement from the machine. Record the subject ID on the tracing and attach to this form as a source document.

Tape or staple flow measurement tracing(s) here.

Surgeon's Signature: _____ Date: _____

SUBJECT ID#: **R**_________
NAME: __________________
TRANSPLANT DATE: __/__/20___

	Native Liver Prior To Recipient Hepatectomy	Graft Immediately After Reperfusion Was any portal vein flow modulation done prior to reperfusion? □ Yes □ No	After Post-Reperfusion Portal Vein Flow Modulation #1 □ Medical modulation □ Splenic artery ligation □ Collateral vein ligation □ Portocaval shunt □ Splenectomy	After Post-Reperfusion Portal Vein Flow Modulation #2 □ Medical modulation □ Splenic artery ligation □ Collateral vein ligation □ Portocaval shunt □ Splenectomy	After Post-Reperfusion Portal Vein Flow Modulation #3 □ Medical modulation □ Splenic artery ligation □ Collateral vein ligation □ Portocaval shunt □ Splenectomy	After Post-Reperfusion Portal Vein Flow Modulation #4 □ Medical modulation □ Splenic artery ligation □ Collateral vein ligation □ Portocaval shunt □ Splenectomy
Hepatic Artery Flow	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured
Portal Vein Flow	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured	Mean: _____ ml/min Min: _____ ml/min Max: _____ ml/min □ Not confident □ Not measured
Portal Vein Pressure	**Clamped:** ____mmHg □ Not measured **Unclamped:** ____mmHg □ Not measured	**Clamped:** ____mmHg □ Not measured **Unclamped:** ____mmHg □ Not measured	**Clamped:** ____mmHg □ Not measured **Unclamped:** ____mmHg □ Not measured	**Clamped:** ____mmHg □ Not measured **Unclamped:** ____mmHg □ Not measured	**Clamped:** ____mmHg □ Not measured **Unclamped:** ____mmHg □ Not measured	**Clamped:** ____mmHg □ Not measured **Unclamped:** ____mmHg □ Not measured
Mean Arterial Pressure	______mmHg	______mmHg	______mmHg	______mmHg	______mmHg	______mmHg
Central Venous Pressure	______mmHg	______mmHg	______mmHg	______mmHg	______mmHg	______mmHg
Cardiac Output	______L/min □ Not measured	______L/min □ Not measured	______L/min □ Not measured	______L/min □ Not measured	______L/min □ Not measured	______L/min □ Not measured

A2ALL2
ADULT TO ADULT LIVING DONOR LIVER
TRANSPLANT STUDY

Patient Study Number: _____

Patient Name: _____

1) In the opinion of the PI, did the subject have small for size syndrome (SFSS)?

Yes

No

2) If the subject had SFSS, did the subject also have any of the following vascular and/or biliary complications?

- Thrombosis or stenosis of the portal vein, hepatic artery, and/or the hepatic vein
- Bile leak and/or stricture

Yes

No

N/A

_____ _____
PI Signature Date

Subject ID #:_____ **Date:**_____

A2ALL-2 Core Study

Degree of Hepatic Encephalopathy

Recipient subjects must have an Encephalopathy Grading Assessment daily on Days 1-13 post transplant, Week 2 (D14) and Month 1.

Time Points

Please check the time point for day of assessment below:

Week 1 Assessment: □D1, □D2, □D3, □D4, □D5, □D6, □D7

Week 2 Assessment: □D8, □D9, □D10, □D11, □D12, □D13, □D14

Month 1 Assessment: □ Month 1

Encephalopathy Grade:

Please assess the subject, and check the encephalopathy grade below to correspond with the day of assessment.

1) The encephalopathy grading scale is as follows:

_____0: None

_____1: Subject intubated/sedated-unable to assess

_____2: Grade 1 – Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction.

_____3: Grade 2 – Lethargy or apathy; minimal disorientation for the time or place; subtle personality change; inappropriate behavior.

_____4: Grade 3 – Somnolence to semi-stupor, but responsive to verbal stimuli; confusion; gross disorientation.

_____5: Grade 4 – Coma (unresponsive to verbal or noxious stimuli).

_____6: Subject is not in hospital – unable to assess

Signature: _____ **Date:** _____

Biopsy Scoring

Ishak Scoring for Fibrosis:

- 0 = No fibrosis
- 1 = Fibrous expansion of some portal areas, with or without short fibrous septa
- 2 = Fibrous expansion of most portal areas, with or without short fibrous septa
- 3 = Fibrous expansion of most portal areas, with occasional portal to portal (p-p) bridging
- 4 = Fibrous expansion of portal areas, with marked bridging (p-p) as well as portal to central (p-c)
- 5 = Marked bridging (p-p and/or p-c) with occasional nodules (incomplete cirrhosis)
- 6 = Cirrhosis; probably or definite
- Not Available

Knodell Necrosis and Inflammation Scoring: Knodell Score for Periportal +/- Bridging Necrosis

- 0 = None
- 1 = Mild piecemeal necrosis
- 3 = Moderate piecemeal necrosis (less than 50% of the circumference of most portal tracts)
- 4 = Marked piecemeal necrosis (more than 50% of the circumference of most portal tracts)
- 5 = Moderate piecemeal necrosis PLUS bridging necrosis
- 6 = Marked piecemeal necrosis PLUS bridging necrosis
- 10 = Multilobular necrosis
- Not Available

Knodell Score for Lobular Inflammation and Focal Necrosis:

- 0 = None
- 1 = Mild (Mild = acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in > 1/3 of lobules or nodules)
- 3 = Moderate (involvement of 1/3 to 2/3 of nodules)
- 4 = Marked (involvement of > 2/3 of lobules or nodules)
- Not Available

Knodell Score for Portal Inflammation:

- 0 = No portal inflammation
- 1 = Mild (sprinkling of inflammatory cells in < 1/3 of portal tracts)
- 3 = Moderate (increased inflammatory cells in 1/3 to 2/3 of portal tracts)
- 4 = Marked (dense packing of inflammatory cells in > 2/3 of portal tracts)
- Not Available

Long-Term Follow-Up (Time 1)*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. Recently you agreed to be contacted by our survey research group for a telephone interview. It has been several years since your liver donation, and we want to learn more about your experience and about how you have been doing recently. You may have participated in earlier surveys, and I'll be asking you questions that may be similar to those you answered before. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all donors' answers in order to learn more about donors' well-being in the years after donation.

First, I have some questions about your opinions and feelings about the living donation process.

1. Looking back on the donation, in terms of the way you felt physically during and after the donation surgery, would you say that the donation was…

   ☐ very stressful ☐ pretty stressful ☐ not very stressful ☐ not at all stressful

2. Thinking about the liver transplant for which you donated, have you felt…

   ☐ very worthwhile ☐ a little worthwhile ☐ not at all worthwhile

3. When thinking about the liver transplant, have you felt…

   ☐ very proud ☐ a little proud ☐ not at all proud

4. When you think about the transplant, have you felt…

   ☐ very brave ☐ a little brave ☐ not at all brave

5. When you think about the transplant, have you felt…

   ☐ very heroic ☐ a little heroic ☐ not at all heroic

6. Since the transplant, would you say you think…

   ☐ more highly of yourself—that you're a better person than before the transplant

   ☐ less highly of yourself, or

   ☐ there is no change in the way you think of yourself

7. How often do you think about having donated a part of your liver? Would you say you think about it…

   ☐ More than once a day ☐ Once a week
   ☐ Once a day ☐ Less often than once a week
   ☐ More than once a week ☐ Never

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8. I'm going to read you some statements about the donation experience. On a scale where 1 indicates that the statement is not at all true and 10 indicates that the statement is very true, tell me how you feel about each statement.

Since the donation…	Not at all true										Very true
a. I feel better about myself.	0	1	2	3	4	5	6	7	8	9	10
b. My family has expressed gratitude to me.	0	1	2	3	4	5	6	7	8	9	10
c. My family seems to hold me in higher esteem.	0	1	2	3	4	5	6	7	8	9	10
d. I feel I have helped my recipient in a significant way.	0	1	2	3	4	5	6	7	8	9	10
e. I feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10
f. My family relationships feel more difficult.	0	1	2	3	4	5	6	7	8	9	10
g. My life has special meaning.	0	1	2	3	4	5	6	7	8	9	10

Now I have some questions about your health since the donation.

9. Physically, how long did it take after the liver donation surgery before you felt completely back to normal? Would you say it took…

☐ 1 week
☐ 2 to 3 weeks
☐ 4 to 5 weeks
☐ 6 to 7 weeks
☐ 2 months
☐ 3 months
☐ 4 months
☐ 5 months
☐ 6 or more months
☐ you still do not feel back to normal

10. Compared to what you expected, would you say that your recovery was slower or faster than expected? Would you say it was…

☐ much slower than expected ☐ slower ☐ as expected ☐ faster ☐ much faster

11. Are there specific physical activities that you can't do as well as before the surgery?

☐ Yes ☐ No

↳ What are they?_____

12. How often do you worry about the physical effects on you of having donated a part of your liver?

☐ Often ☐ sometimes ☐ almost never

13. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

14. the past year, have you developed any medical problems that you think are related to the donation surgery?

☐ Yes ☐ No

↳ please describe _____

15. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

16. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

17. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

18. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if <u>your health now</u> limits you a lot, limits you a little, or does not limit you at all in these activities.
[IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing <u>several</u> flights of stairs	_____	_____	_____
e.	Climbing <u>one</u> flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking <u>more than a mile</u>	_____	_____	_____
h.	Walking <u>several hundred yards</u>	_____	_____	_____

i. Walking one hundred yards	_____	_____	_____
j. Bathing or dressing yourself	_____	_____	_____

19. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

20. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

21. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

22. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

23. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

24. The next questions are about how you feel and how things have been with you during the past 4

weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

25. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? Has it interfered…

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

26. Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

27. Here is a list of ways some people may feel physically after living organ donation. For each, please tell me if you have had the problem a lot, a little, or not at all in the past month.

	A LOT	A LITTLE	NOT AT ALL
a. Light headedness	1	2	3
b. Weakness	1	2	3
c. Tiredness	1	2	3
d. Bleeding at the site of the surgery	1	2	3

	A LOT	A LITTLE	NOT AT ALL
e. Pain at the site of the surgery	1	2	3
f. Itching at the site of the surgery	1	2	3
g. Tension around the site of the surgery	1	2	3
h. Numbness around the site of the surgery	1	2	3
i. Abdominal pain	1	2	3
j. Low back pain	1	2	3
k. Abdominal bloating or swelling	1	2	3
l. Decreased stomach tone	1	2	3
m. Puffiness in hands or feet	1	2	3
n. Leg swelling	1	2	3
o. Difficulty walking	1	2	3
p. Problems sleeping	1	2	3
q. Nausea or vomiting	1	2	3
r. Problems eating	1	2	3
s. Infection at the site of the surgery	1	2	3

28. I've asked you some general questions about pain. Now think about just the past 24 hours. In the **past 24 hours**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 29. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **past 24 hours**, pain has interfered with your:

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

29. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way <u>in the past week</u>.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

I'd like to turn now to how things have been with the transplant recipient and with other people.

30. First, what is your connection to the liver recipient? ***(RECORD WHETHER THE RECIPIENT IS THE DONOR'S SIBLING, PARENT, SPOUSE, FRIEND, ETC.)***:

    Recipient is _____

31. How often do you think about your liver recipient, on average? Would you say it is…

    □ More than once a day □ Two or three times a month
    □ Once a day □ Once a month
    □ More than once a week □ Less than once a month

32. Is your liver recipient currently: □ alive □ no longer alive, or □ you don't know

IF RECIPIENT IS NO LONGER ALIVE:

a. How long after the donation did your recipient die?_____

b. Have you sought counseling since the death of your recipient? □ yes □ no

c. Thinking about your recipient's death, please tell me about how you feel about the outcome: On a 10 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "10" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you rate how you feel about the outcome

Not at all guilty	1	2	3	4	5	6	7	8	9	10	very guilty
Not at all responsible	1	2	3	4	5	6	7	8	9	10	very responsible

IF RECIPIENT IS ALIVE:

d. How worried are you about your recipient?

□ very worried □ pretty worried □ not very worried □ not at all worried

e. How many times have you seen your recipient in the past year? _____ times

f. Would you like more contact or communication with your recipient?

□ yes, a lot more □ yes, a little more □ no

g. I'm going to read you some words that might describe your interactions with your liver recipient since the transplant. On a 7 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "7" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you describe your interactions with your liver recipient since the transplant?

Rewarding	1	2	3	4	5	6	7	Disappointing
Comfortable	1	2	3	4	5	6	7	Uncomfortable
Hard	1	2	3	4	5	6	7	Easy
Positive	1	2	3	4	5	6	7	Negative
Tense	1	2	3	4	5	6	7	Relaxed
Close	1	2	3	4	5	6	7	Distant
Awkward	1	2	3	4	5	6	7	Natural

h. Did your relationship with the recipient change after the transplant? Is your relationship with the recipient now…

□ much worse □ worse □ the same □ better □ much better

i. How would you rate the overall quality of your relationship with your recipient at this time? Would you say it is…

□ excellent □ very good □ average □ fair □ poor

j. Do you agree or disagree with this statement? "I feel closer to the recipient than I did before the transplant." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

k. Do you agree or disagree with this statement? "The recipient of my liver behaves in a way that risks the continued healthy functioning of the donated liver." Would you say you…

□ strongly agree □ agree □ neither agree nor disagree □ disagree □ strongly disagree

33. Compared to before the transplant, has your relationship with the rest of your family changed? Would you say it has…

□ Improved greatly
□ Improved somewhat
□ Stayed the same
□ Gotten somewhat worse

☐ Gotten much worse

34. What about any relationship you have with a spouse or partner. First, what is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

35. ***[IF PARTICIPANT IS MARRIED/ LIVING WITH PARTNER AND SPOUSE/PARTNER IS NOT THE TRANSPLANT RECIPIENT AS PER ITEM #30 ABOVE]:*** If you were married to or living with this person at the time of your donation, has your relationship with him/her changed, compared to before the transplant? Has it…

☐ Improved greatly
☐ Improved somewhat
☐ Stayed the same
☐ Gotten somewhat worse
☐ Gotten much worse
☐ Not applicable: was not married/living with this person at the time of the transplant

36. The next questions focus on how the donation experience may have affected you. I'm going to read you a list of ways people sometimes feel after having donated a part of their liver for transplantation. Please tell me if you agree a lot, agree a little, disagree a little or disagree a lot with each statement.

a. Being a liver donor makes a person feel that he/she is somehow a bigger and more worthwhile person. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
b. A person willing to donate part of their liver is almost a hero. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
c. Donating a part of my liver was really sort of a high point in my life, making everything seem more meaningful. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

37. Please tell me if you experienced any of the following as a result of the donation, where a zero means you did not experience it, up to a 5, meaning that you experienced it to a very great degree.

	Did not experience this					Experienced this to a very great degree
a. I changed my priorities about what is important in life.	0	1	2	3	4	5
b. I have a greater appreciation for the value of	0	1	2	3	4	5

	Did not experience this					Experienced this to a very great degree
my own life.						
c. I am able to do better things with my life.	0	1	2	3	4	5
d. I have a better understanding of spiritual matters.	0	1	2	3	4	5
e. I have a greater sense of closeness with others.	0	1	2	3	4	5
f. I established a new path for my life.	0	1	2	3	4	5
g. I know better that I can handle difficulties.	0	1	2	3	4	5
h. I have a stronger religious faith.	0	1	2	3	4	5
i. I discovered that I'm stronger than I thought I was.	0	1	2	3	4	5
j. I learned a great deal about how wonderful people are.	0	1	2	3	4	5

Now I'd like to focus on how you've been feeling recently.

38. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

    complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

39. Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Little interest or pleasure in doing things.	1	2	3	4
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

40. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 41. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

41. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 42.

Have any of the following happened to you more than once in the last 6 months?

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

The next questions are about how you have dealt with financial issues related to your liver donation.

42. First, are you currently employed (in a paid position)?

- ☐ Working full time
- ☐ Working part time by choice
- ☐ Working part time due to disease or illness
- ☐ Not working due to disease or illness
- ☐ Not working because you can't find a job
- ☐ Retired

43. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

44. Did you have to permanently change jobs or modify your work because of your liver donation?

- ☐ No
- ☐ Yes, to a job with less manual labor
- ☐ Yes, to a less demanding or stressful job
- ☐ Yes, other changes: please describe:_____
- ☐ Not applicable because not employed before donation

45. Did you have any permanent changes in your income because of your liver donation?

☐ No, it was not changed ☐ Yes, it decreased ☐ Yes, it increased

46. Did you have expenses related to your liver donation that were not covered by insurance? Tell me if, at any time since the donation, you have had any of the following expenses due to the donation. ***(CHECK ALL THAT APPLY)***

- ☐ Lost wages
- ☐ Child or family members' care
- ☐ Transportation or parking costs
- ☐ Housing or lodging costs
- ☐ Food costs
- ☐ Medication costs not covered by any insurance
- ☐ Medical bills not covered by any insurance
- ☐ Other costs (list: _____)

47. Overall, how have the costs related to the donation compared to what you expected?

☐ less than expected ☐ more than expected ☐ about what was expected

48. Overall, have the costs related to the donation been a significant financial burden for you?

☐ No, not a burden ☐ Yes, a mild burden ☐ Yes, a moderate burden ☐ Yes, a severe burden

49. At any time since the donation, have you had any of the following insurance problems because of the donation?

a. Did you have trouble keeping the health insurance that you already had?

- ☐ no
- ☐ yes, I had trouble but was able to keep my insurance
- ☐ yes, I lost my health insurance as a result of the donation
- ☐ not applicable (did not have insurance)

b. Did you have trouble getting new health insurance because of the donation?

- ☐ no
- ☐ yes, I had trouble but was able to get new insurance
- ☐ yes, I was denied new health insurance
- ☐ not applicable (did not try to get new health insurance)

c. Did you have trouble keeping the life insurance you already had because of the donation?

- ☐ no
- ☐ yes, I had trouble but was able to keep my life insurance
- ☐ yes, I lost my life insurance
- ☐ not applicable (did not have life insurance)

d. Did you have trouble getting new life insurance because of the donation?

- ☐ no
- ☐ yes, I had trouble but was able to get new life insurance
- ☐ yes, I was denied new life insurance
- ☐ not applicable (did not try to get new life insurance)

50. What type of medical insurance do you currently have? Please list all sources of coverage (for example, Medicare, Medicaid, private insurance, insurance through another family member, donation-related insurance).

_____

I have few questions about what you expect in the future. Here are some concerns that people sometimes have after donating an organ for transplantation. Please tell me tell me about whether you have any of these concerns.

51. How strongly do you agree or disagree with this statement: "Sometimes I worry that the liver donation will have negative effects on my health in the future." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

52. How strongly do you agree or disagree with this statement: "Since my liver donation, I worry that I will never feel physically 100% well again." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

53. How strongly do you agree or disagree with this statement: "Knowing what I know now, I would donate again." Would you say you…

☐ strongly agree ☐ agree ☐ are unsure ☐ disagree ☐ strongly disagree

54. How would you rate your overall feelings about your liver donation? Would you say they are…

☐ Very positive ☐ Somewhat positive ☐ A little positive ☐ Neither positive nor negative ☐ A little negative ☐ Very negative

55. Do you somehow feel like a better person after having donated a part of your liver?

☐ yes ☐ no

56. Here is a list of ways some people feel about liver donors. Tell me which is the closest to the way you would describe a living liver donor.

☐ anyone who donated part of their liver could be called a hero

☐ a person who donates part of their liver makes an exceptional sacrifice

☐ anyone who donates part of their liver makes a sacrifice somewhat out of the ordinary

☐ it is generous to give part of your liver but anyone should do as much

Lastly, I have few standard background questions.

57. How far did you go in school?

☐ grammar school (grades 1 - 6)
☐ junior high school (through 9th grade)
☐ some high school (grades 10 - 11)
☐ high school graduate
☐ vocational school or some college
☐ college graduate
☐ some graduate school
☐ graduate or professional degree

58. Which of the following best describes the ethnic group to which you belong? ***(TO BE ASKED ONLY OF RESPONDENTS FROM THE 3 NEW A2ALL SITES)***

First, are you: ☐ Hispanic/Latino ☐ Not Hispanic/Latino

Second, are you: (If your parents belong to different groups, tell me all that apply)

☐ White (European American)
☐ Black (Caribbean or African descent)
☐ Asian/Pacific Islander (Chinese, Japanese, Korean, etc.)
☐ Hawaiian/Pacific Islander (Filipino, Indonesian, Hawaiian, etc.)
☐ Native American or Alaska Native
☐ Other (specify:_____)

59. How many people usually live in your home, <u>including</u> yourself? ___ people

60. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, tell me to stop when I get to the right one.

☐ $10,000 or less	☐ $70,000 or less	☐ $130,000 or less
☐ $20,000 or less	☐ $80,000 or less	☐ $140,000 or less
☐ $30,000 or less	☐ $90,000 or less	☐ $150,000 or less
☐ $40,000 or less	☐ $100,000 or less	☐ more than $150,000
☐ $50,000 or less	☐ $110,000 or less	
☐ $60,000 or less	☐ $120,000 or less	

61. Is there anything else that you think would be important for us to know about how you've been doing since the donation?

_____

_____

_____

Thank you!

We'll put your $20 payment in the mail and we'll be calling you back next year for an update on how you're doing.

Long-Term Follow-Up (Time 2)*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. We called you a year ago and I'm calling again today to update some information from last year. We want to learn about how you have been doing in the past year. I'll be asking you questions that are similar to those you answered last year. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all donors' answers in order to learn more about donors' well-being in the years after donation.

First, I have some questions about your opinions and feelings about the living donation process.

7. Looking back on the donation, in terms of the way you felt physically during and after the donation surgery, would you say that the donation was…

☐ very stressful ☐ pretty stressful ☐ not very stressful ☐ not at all stressful

8. Thinking about the liver transplant for which you donated, have you felt…

☐ very worthwhile ☐ a little worthwhile ☐ not at all worthwhile

9. When thinking about the liver transplant, have you felt…

☐ very proud ☐ a little proud ☐ not at all proud

10. When you think about the transplant, have you felt…

☐ very brave ☐ a little brave ☐ not at all brave

11. When you think about the transplant, have you felt…

☐ very heroic ☐ a little heroic ☐ not at all heroic

12. Since the transplant, would you say you think…

☐ more highly of yourself—that you're a better person than before the transplant

☐ less highly of yourself, or

☐ there is no change in the way you think of yourself

7. How often do you think about having donated a part of your liver? Would you say you think about it…

☐ More than once a day ☐ Once a week
☐ Once a day ☐ Less often than once a week
☐ More than once a week ☐ Never

8. I'm going to read you some statements about the donation experience. On a scale where 1 indicates that the statement is not at all true and 10 indicates that the statement is very true, tell me how you feel about each statement.

Since the donation…	Not at all true										Very true
a. I feel better about myself.	0	1	2	3	4	5	6	7	8	9	10
b. My family has expressed gratitude to me.	0	1	2	3	4	5	6	7	8	9	10
c. My family seems to hold me in higher esteem.	0	1	2	3	4	5	6	7	8	9	10
d. I feel I have helped my recipient in a significant way.	0	1	2	3	4	5	6	7	8	9	10
e. I feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10
f. My family relationships feel more difficult.	0	1	2	3	4	5	6	7	8	9	10
g. My life has special meaning.	0	1	2	3	4	5	6	7	8	9	10

Now I have some questions about your health since the donation.

9. Physically, do you now feel completely back to normal?

☐ yes ☐ no

10. Are there specific physical activities that you can't do as well as before the surgery?

☐ Yes ☐ No

↳ What are they?_____

11. How often do you worry about the physical effects on you of having donated a part of your liver?

☐ often ☐ sometimes ☐ almost never

12. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

13. In the past year, have you developed any medical problems that you think are related to the donation surgery?

☐ Yes ☐ No

↳

please describe _____

14. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

15. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

16. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

17. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if <u>your health now</u> limits you a lot, limits you a little, or does not limit you at all in these activities.
[IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing <u>several</u> flights of stairs	_____	_____	_____
e.	Climbing <u>one</u> flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking <u>more than a mile</u>	_____	_____	_____
h.	Walking <u>several hundred yards</u>	_____	_____	_____
i.	Walking <u>one hundred yards</u>	_____	_____	_____
j.	Bathing or dressing yourself	_____	_____	_____

18. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

19. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

21. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

23. The next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

24. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)? Has it interfered…

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

25. Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

26. Here is a list of ways some people may feel physically after living organ donation. For each, please tell me if you have had the problem a lot, a little, or not at all <u>in the past month</u>.

	A LOT	A LITTLE	NOT AT ALL
a. Light headedness	1	2	3
b. Weakness	1	2	3
c. Tiredness	1	2	3
d. Bleeding at the site of the surgery	1	2	3
e. Pain at the site of the surgery	1	2	3
f. Itching at the site of the surgery	1	2	3

	A LOT	A LITTLE	NOT AT ALL
g. Tension around the site of the surgery	1	2	3
h. Numbness around the site of the surgery	1	2	3
i. Abdominal pain	1	2	3
j. Low back pain	1	2	3
k. Abdominal bloating or swelling	1	2	3
l. Decreased stomach tone	1	2	3
m. Puffiness in hands or feet	1	2	3
n. Leg swelling	1	2	3
o. Difficulty walking	1	2	3
p. Problems sleeping	1	2	3
q. Nausea or vomiting	1	2	3
r. Problems eating	1	2	3
s. Infection at the site of the surgery	1	2	3

27. I've asked you some general questions about pain. Now think about just the past 24 hours. In the **past 24 hours**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 28. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **past 24 hours**, pain has interfered with your:

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

28. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way <u>in the past week</u>.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

I'd like to turn now to how things have been with the transplant recipient and with other people.

29. First, what is your connection to the liver recipient? ***(RECORD WHETHER THE RECIPIENT IS THE DONOR'S SIBLING, PARENT, SPOUSE, FRIEND, ETC.)***:

    Recipient is _____

30. How often do you think about your liver recipient, on average? Would you say it is…

    □ More than once a day □ Two or three times a month
    □ Once a day □ Once a month
    □ More than once a week □ Less than once a month

31. Is your liver recipient currently: □ alive □ no longer alive, or □ you don't know

IF RECIPIENT IS NO LONGER ALIVE:

a. How long after the donation did your recipient die?_____

b. Have you sought counseling since the death of your recipient? □ yes □ no

c. Thinking about your recipient's death, please tell me about how you feel about the outcome: On a 10 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "10" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you rate how you feel about the outcome

Not at all guilty	1	2	3	4	5	6	7	8	9	10	very guilty
Not at all responsible	1	2	3	4	5	6	7	8	9	10	very responsible

IF RECIPIENT IS ALIVE:

d. How worried are you about your recipient?

□ very worried □ pretty worried □ not very worried □ not at all worried

e. How many times have you seen your recipient in the past year? _____ times

f. Would you like more contact or communication with your recipient?

□ yes, a lot more □ yes, a little more □ no

h. I'm going to read you some words that might describe your interactions with your liver recipient since the transplant. On a 7 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "7" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you describe your interactions with your liver recipient since the transplant?

Rewarding	1	2	3	4	5	6	7	Disappointing
Comfortable	1	2	3	4	5	6	7	Uncomfortable
Hard	1	2	3	4	5	6	7	Easy
Positive	1	2	3	4	5	6	7	Negative
Tense	1	2	3	4	5	6	7	Relaxed
Close	1	2	3	4	5	6	7	Distant
Awkward	1	2	3	4	5	6	7	Natural

h. Did your relationship with the recipient change after the transplant? Is your relationship with the recipient now…

□ much worse □ worse □ the same □ better □ much better

i. How would you rate the overall quality of your relationship with your recipient at this time? Would you say it is…

□ excellent □ very good □ average □ fair □ poor

j. Do you agree or disagree with this statement? "I feel closer to the recipient than I did before the transplant." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

l. Do you agree or disagree with this statement? "The recipient of my liver behaves in a way that risks the continued healthy functioning of the donated liver." Would you say you…

□ strongly agree □ agree □ neither agree nor disagree □ disagree □ strongly disagree

32. Compared to before the transplant, has your relationship with the rest of your family changed? Would you say it has…

□ Improved greatly
□ Improved somewhat
□ Stayed the same
□ Gotten somewhat worse

☐ Gotten much worse

38. What about any relationship you have with a spouse or partner. First, what is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

39. ***[IF PARTICIPANT IS MARRIED/ LIVING WITH PARTNER AND SPOUSE/PARTNER IS NOT THE TRANSPLANT RECIPIENT AS PER ITEM #29 ABOVE]:*** If you were married to or living with this person at the time of your donation, has your relationship with him/her changed, compared to before the transplant? Has it…

☐ Improved greatly
☐ Improved somewhat
☐ Stayed the same
☐ Gotten somewhat worse
☐ Gotten much worse
☐ Not applicable: was not married/living with this person at the time of the transplant

40. The next questions focus on how the donation experience may have affected you. I'm going to read you a list of ways people sometimes feel after having donated a part of their liver for transplantation. Please tell me if you agree a lot, agree a little, disagree a little or disagree a lot with each statement.

a. Being a liver donor makes a person feel that he/she is somehow a bigger and more worthwhile person. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
b. A person willing to donate part of their liver is almost a hero. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
c. Donating a part of my liver was really sort of a high point in my life, making everything seem more meaningful. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

41. Please tell me if you experienced any of the following as a result of the donation, where a zero means you did not experience it, up to a 5, meaning that you experienced it to a very great degree.

	Did not experience this					Experienced this to a very great degree
a. I changed my priorities about what is important in life.	0	1	2	3	4	5
b. I have a greater appreciation for the value of	0	1	2	3	4	5

	Did not experience this					Experienced this to a very great degree
my own life.						
c. I am able to do better things with my life.	0	1	2	3	4	5
d. I have a better understanding of spiritual matters.	0	1	2	3	4	5
e. I have a greater sense of closeness with others.	0	1	2	3	4	5
f. I established a new path for my life.	0	1	2	3	4	5
g. I know better that I can handle difficulties.	0	1	2	3	4	5
h. I have a stronger religious faith.	0	1	2	3	4	5
i. I discovered that I'm stronger than I thought I was.	0	1	2	3	4	5
j. I learned a great deal about how wonderful people are.	0	1	2	3	4	5

Now I'd like to focus on how you've been feeling recently.

37. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

    complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

38. Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Little interest or pleasure in doing things.	1	2	3	4
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

39. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 40. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

40. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 41.

Have any of the following happened to you more than once in the last 6 months?

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

The next questions are about how you have dealt with financial issues related to your liver donation.

41. First, are you currently employed (in a paid position)?

- ☐ Working full time
- ☐ Working part time by choice
- ☐ Working part time due to disease or illness
- ☐ Not working due to disease or illness
- ☐ Not working because you can't find a job
- ☐ Retired

42. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

43. Have you had to change jobs or modify your work <u>in the past year</u> because of your liver donation?

- ☐ No
- ☐ Yes, to a job with less manual labor
- ☐ Yes, to a less demanding or stressful job
- ☐ Yes, other changes: please describe:_____
- ☐ Not applicable because you have been unemployed for longer than the past year

44. <u>In the past year</u>, have you had any changes in your income because of your liver donation?

☐ No, it was not changed ☐ Yes, it decreased ☐ Yes, it increased

45. <u>In the past year</u>, have you had expenses related to your liver donation that were not covered by insurance? Tell me if you have had any of the following expenses due to the donation. ***(CHECK ALL THAT APPLY)***

- ☐ Lost wages
- ☐ Child or family members' care
- ☐ Transportation or parking costs
- ☐ Housing or lodging costs
- ☐ Food costs
- ☐ Medication costs not covered by any insurance
- ☐ Medical bills not covered by any insurance
- ☐ Other costs (list: _____)

46. Overall, across all of the years since donation, how have the costs related to the donation compared to what you expected?

☐ less than expected ☐ more than expected ☐ about what was expected

47. Overall, have the costs related to the donation been a significant financial burden for you?

☐ No, not a burden ☐ Yes, a mild burden ☐ Yes, a moderate burden ☐ Yes, a severe burden

48. <u>In the past year</u>, have you had any of the following insurance problems because of the donation?

c. Did you have trouble keeping the health insurance that you already had?

- ☐ no
- ☐ yes, I had trouble but was able to keep my insurance
- ☐ yes, I lost my health insurance as a result of the donation
- ☐ not applicable (did not have insurance)

d. Did you have trouble getting new health insurance because of the donation?

- ☐ no
- ☐ yes, I had trouble but was able to get new insurance
- ☐ yes, I was denied new health insurance
- ☐ not applicable (did not try to get new health insurance)

c. Did you have trouble keeping the life insurance you already had because of the donation?

- ☐ no
- ☐ yes, I had trouble but was able to keep my life insurance
- ☐ yes, I lost my life insurance
- ☐ not applicable (did not have life insurance)

d. Did you have trouble getting new life insurance because of the donation?

- ☐ no
- ☐ yes, I had trouble but was able to get new life insurance
- ☐ yes, I was denied new life insurance
- ☐ not applicable (did not try to get new life insurance)

49. What type of medical insurance do you currently have? Please list all sources of coverage (for example, Medicare, Medicaid, private insurance, insurance through another family member, donation-related insurance).

_____

I have few questions about what you expect in the future. Here are some concerns that people sometimes have after donating an organ for transplantation. Please tell me tell me about whether you have any of these concerns.

50. How strongly do you agree or disagree with this statement: "Sometimes I worry that the liver donation will have negative effects on my health in the future." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

51. How strongly do you agree or disagree with this statement: "Since my liver donation, I worry that I will never feel physically 100% well again." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

52. How strongly do you agree or disagree with this statement: "Knowing what I know now, I would donate again." Would you say you…

☐ strongly agree ☐ agree ☐ are unsure ☐ disagree ☐ strongly disagree

53. How would you rate your overall feelings about your liver donation? Would you say they are…

☐ Very positive ☐ Somewhat positive ☐ A little positive ☐ Neither positive nor negative ☐ A little negative ☐ Very negative

57. Do you somehow feel like a better person after having donated a part of your liver?

☐ yes ☐ no

58. Here is a list of ways some people feel about liver donors. Tell me which is the closest to the way you would describe a living liver donor.

☐ anyone who donated part of their liver could be called a hero

☐ a person who donates part of their liver makes an exceptional sacrifice

☐ anyone who donates part of their liver makes a sacrifice somewhat out of the ordinary

☐ it is generous to give part of your liver but anyone should do as much

Lastly, I have few standard background questions.

56. How many people usually live in your home, <u>including</u> yourself? ___ people

57. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, <u>tell me to stop when I get to the right one</u>.

☐ $10,000 or less
☐ $20,000 or less
☐ $30,000 or less
☐ $40,000 or less
☐ $50,000 or less
☐ $60,000 or less
☐ $70,000 or less
☐ $80,000 or less
☐ $90,000 or less
☐ $100,000 or less
☐ $110,000 or less
☐ $120,000 or less
☐ $130,000 or less
☐ $140,000 or less
☐ $150,000 or less
☐ more than $150,000

58. Is there anything else that you think would be important for us to know about how you've been doing since the donation?

_____

_____

_____

Thank you!

We'll put your $20 payment in the mail and we'll be calling you back next year for an update on how you're doing.

Long-Term Follow-Up (Time 3)*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. We called you a year ago and I'm calling again today to update some information from last year. We want to learn about how you have been doing in the past year. I'll be asking you questions that are similar to those you answered last year. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all donors' answers in order to learn more about donors' well-being in the years after donation.

First, I have some questions about your opinions and feelings about the living donation process.

13. Looking back on the donation, in terms of the way you felt physically during and after the donation surgery, would you say that the donation was…

☐ very stressful ☐ pretty stressful ☐ not very stressful ☐ not at all stressful

14. Thinking about the liver transplant for which you donated, have you felt…

☐ very worthwhile ☐ a little worthwhile ☐ not at all worthwhile

15. When thinking about the liver transplant, have you felt…

☐ very proud ☐ a little proud ☐ not at all proud

16. When you think about the transplant, have you felt…

☐ very brave ☐ a little brave ☐ not at all brave

17. When you think about the transplant, have you felt…

☐ very heroic ☐ a little heroic ☐ not at all heroic

18. Since the transplant, would you say you think…

☐ more highly of yourself—that you're a better person than before the transplant

☐ less highly of yourself, or

☐ there is no change in the way you think of yourself

7. How often do you think about having donated a part of your liver? Would you say you think about it…

☐ More than once a day ☐ Once a week
☐ Once a day ☐ Less often than once a week
☐ More than once a week ☐ Never

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8. I'm going to read you some statements about the donation experience. On a scale where 1 indicates that the statement is not at all true and 10 indicates that the statement is very true, tell me how you feel about each statement.

Since the donation…	Not at all true										Very true
a. I feel better about myself.	0	1	2	3	4	5	6	7	8	9	10
b. My family has expressed gratitude to me.	0	1	2	3	4	5	6	7	8	9	10
c. My family seems to hold me in higher esteem.	0	1	2	3	4	5	6	7	8	9	10
d. I feel I have helped my recipient in a significant way.	0	1	2	3	4	5	6	7	8	9	10
e. I feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10
f. My family relationships feel more difficult.	0	1	2	3	4	5	6	7	8	9	10
g. My life has special meaning.	0	1	2	3	4	5	6	7	8	9	10

Now I have some questions about your health since the donation.

9. Physically, do you now feel completely back to normal?

☐ yes ☐ no

10. Are there specific physical activities that you can't do as well as before the surgery?

☐ Yes ☐ No

↳ What are they?_____

11. How often do you worry about the physical effects on you of having donated a part of your liver?

☐ often ☐ sometimes ☐ almost never

14. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

15. In the past year, have you developed any medical problems that you think are related to the donation surgery?

☐ Yes ☐ No

↳

please describe _____

14. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

20. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

21. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

22. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if <u>your health now</u> limits you a lot, limits you a little, or does not limit you at all in these activities.
[IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing <u>several</u> flights of stairs	_____	_____	_____
e.	Climbing <u>one</u> flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking <u>more than a mile</u>	_____	_____	_____
h.	Walking <u>several hundred yards</u>	_____	_____	_____
i.	Walking <u>one hundred yards</u>	_____	_____	_____
j.	Bathing or dressing yourself	_____	_____	_____

23. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

24. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

21. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

24. The next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

24. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)? Has it interfered…

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

25. Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

26. Here is a list of ways some people may feel physically after living organ donation. For each, please tell me if you have had the problem a lot, a little, or not at all <u>in the past month</u>.

	A LOT	A LITTLE	NOT AT ALL
a. Light headedness	1	2	3
b. Weakness	1	2	3
c. Tiredness	1	2	3
d. Bleeding at the site of the surgery	1	2	3
e. Pain at the site of the surgery	1	2	3
f. Itching at the site of the surgery	1	2	3

	A LOT	A LITTLE	NOT AT ALL
g. Tension around the site of the surgery	1	2	3
h. Numbness around the site of the surgery	1	2	3
i. Abdominal pain	1	2	3
j. Low back pain	1	2	3
k. Abdominal bloating or swelling	1	2	3
l. Decreased stomach tone	1	2	3
m. Puffiness in hands or feet	1	2	3
n. Leg swelling	1	2	3
o. Difficulty walking	1	2	3
p. Problems sleeping	1	2	3
q. Nausea or vomiting	1	2	3
r. Problems eating	1	2	3
s. Infection at the site of the surgery	1	2	3

27. I've asked you some general questions about pain. Now think about just the past 24 hours. In the **past 24 hours**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 28. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **past 24 hours**, pain has interfered with your:

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

28. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way <u>in the past week</u>.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

I'd like to turn now to how things have been with the transplant recipient and with other people.

30. First, what is your connection to the liver recipient? ***(RECORD WHETHER THE RECIPIENT IS THE DONOR'S SIBLING, PARENT, SPOUSE, FRIEND, ETC.)***:

    Recipient is _____

30. How often do you think about your liver recipient, on average? Would you say it is…

- □ More than once a day
- □ Once a day
- □ More than once a week
- □ Two or three times a month
- □ Once a month
- □ Less than once a month

31. Is your liver recipient currently: □ alive □ no longer alive, or □ you don't know

IF RECIPIENT IS NO LONGER ALIVE:

a. How long after the donation did your recipient die?_____

b. Have you sought counseling since the death of your recipient? □ yes □ no

c. Thinking about your recipient's death, please tell me about how you feel about the outcome: On a 10 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "10" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you rate how you feel about the outcome

Not at all guilty	1	2	3	4	5	6	7	8	9	10	very guilty
Not at all responsible	1	2	3	4	5	6	7	8	9	10	very responsible

IF RECIPIENT IS ALIVE:

d. How worried are you about your recipient?

□ very worried □ pretty worried □ not very worried □ not at all worried

e. How many times have you seen your recipient in the past year? _____ times

f. Would you like more contact or communication with your recipient?

□ yes, a lot more □ yes, a little more □ no

i. I'm going to read you some words that might describe your interactions with your liver recipient since the transplant. On a 7 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "7" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you describe your interactions with your liver recipient since the transplant?

Rewarding	1	2	3	4	5	6	7	Disappointing
Comfortable	1	2	3	4	5	6	7	Uncomfortable
Hard	1	2	3	4	5	6	7	Easy
Positive	1	2	3	4	5	6	7	Negative
Tense	1	2	3	4	5	6	7	Relaxed
Close	1	2	3	4	5	6	7	Distant
Awkward	1	2	3	4	5	6	7	Natural

h. Did your relationship with the recipient change after the transplant? Is your relationship with the recipient now…

□ much worse □ worse □ the same □ better □ much better

i. How would you rate the overall quality of your relationship with your recipient at this time? Would you say it is…

□ excellent □ very good □ average □ fair □ poor

j. Do you agree or disagree with this statement? "I feel closer to the recipient than I did before the transplant." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

m. Do you agree or disagree with this statement? "The recipient of my liver behaves in a way that risks the continued healthy functioning of the donated liver." Would you say you…

□ strongly agree □ agree □ neither agree nor disagree □ disagree □ strongly disagree

33. Compared to before the transplant, has your relationship with the rest of your family changed? Would you say it has…

□ Improved greatly
□ Improved somewhat
□ Stayed the same
□ Gotten somewhat worse

☐ Gotten much worse

42. What about any relationship you have with a spouse or partner. First, what is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

43. ***[IF PARTICIPANT IS MARRIED/ LIVING WITH PARTNER AND SPOUSE/PARTNER IS NOT THE TRANSPLANT RECIPIENT AS PER ITEM #29 ABOVE]:*** If you were married to or living with this person at the time of your donation, has your relationship with him/her changed, compared to before the transplant? Has it…

☐ Improved greatly
☐ Improved somewhat
☐ Stayed the same
☐ Gotten somewhat worse
☐ Gotten much worse
☐ Not applicable: was not married/living with this person at the time of the transplant

44. The next questions focus on how the donation experience may have affected you. I'm going to read you a list of ways people sometimes feel after having donated a part of their liver for transplantation. Please tell me if you agree a lot, agree a little, disagree a little or disagree a lot with each statement.

a. Being a liver donor makes a person feel that he/she is somehow a bigger and more worthwhile person. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
b. A person willing to donate part of their liver is almost a hero. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
c. Donating a part of my liver was really sort of a high point in my life, making everything seem more meaningful. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

45. Please tell me if you experienced any of the following as a result of the donation, where a zero means you did not experience it, up to a 5, meaning that you experienced it to a very great degree.

	Did not experience this					Experienced this to a very great degree
a. I changed my priorities about what is important in life.	0	1	2	3	4	5
b. I have a greater appreciation for the value of	0	1	2	3	4	5

	Did not experience this					Experienced this to a very great degree
my own life.						
c. I am able to do better things with my life.	0	1	2	3	4	5
d. I have a better understanding of spiritual matters.	0	1	2	3	4	5
e. I have a greater sense of closeness with others.	0	1	2	3	4	5
f. I established a new path for my life.	0	1	2	3	4	5
g. I know better that I can handle difficulties.	0	1	2	3	4	5
h. I have a stronger religious faith.	0	1	2	3	4	5
i. I discovered that I'm stronger than I thought I was.	0	1	2	3	4	5
j. I learned a great deal about how wonderful people are.	0	1	2	3	4	5

Now I'd like to focus on how you've been feeling recently.

37. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

    complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

39. Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Little interest or pleasure in doing things.	1	2	3	4
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

39. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 40. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

40. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 41.

Have any of the following happened to you more than once in the last 6 months?

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

The next questions are about how you have dealt with financial issues related to your liver donation.

41. First, are you currently employed (in a paid position)?

- ☐ Working full time
- ☐ Working part time by choice
- ☐ Working part time due to disease or illness
- ☐ Not working due to disease or illness
- ☐ Not working because you can't find a job
- ☐ Retired

42. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

46. Have you had to change jobs or modify your work <u>in the past year</u> because of your liver donation?

- ☐ No
- ☐ Yes, to a job with less manual labor
- ☐ Yes, to a less demanding or stressful job
- ☐ Yes, other changes: please describe:_____
- ☐ Not applicable because you have been unemployed for longer than the past year

47. <u>In the past year</u>, have you had any changes in your income because of your liver donation?

☐ No, it was not changed ☐ Yes, it decreased ☐ Yes, it increased

48. <u>In the past year</u>, have you had expenses related to your liver donation that were not covered by insurance? Tell me if you have had any of the following expenses due to the donation. ***(CHECK ALL THAT APPLY)***

- ☐ Lost wages
- ☐ Child or family members' care
- ☐ Transportation or parking costs
- ☐ Housing or lodging costs
- ☐ Food costs
- ☐ Medication costs not covered by any insurance
- ☐ Medical bills not covered by any insurance
- ☐ Other costs (list: _____)

46. Overall, across all of the years since donation, how have the costs related to the donation compared to what you expected?

☐ less than expected ☐ more than expected ☐ about what was expected

47. Overall, have the costs related to the donation been a significant financial burden for you?

☐ No, not a burden ☐ Yes, a mild burden ☐ Yes, a moderate burden ☐ Yes, a severe burden

49. <u>In the past year</u>, have you had any of the following insurance problems because of the donation?

e. Did you have trouble keeping the health insurance that you already had?

☐ no ☐ yes, I had trouble but was able to keep my insurance ☐ yes, I lost my health insurance as a result of the donation ☐ not applicable (did not have insurance)
f. Did you have trouble getting new health insurance because of the donation? ☐ no ☐ yes, I had trouble but was able to get new insurance ☐ yes, I was denied new health insurance ☐ not applicable (did not try to get new health insurance)
c. Did you have trouble keeping the life insurance you already had because of the donation? ☐ no ☐ yes, I had trouble but was able to keep my life insurance ☐ yes, I lost my life insurance ☐ not applicable (did not have life insurance)
d. Did you have trouble getting new life insurance because of the donation? ☐ no ☐ yes, I had trouble but was able to get new life insurance ☐ yes, I was denied new life insurance ☐ not applicable (did not try to get new life insurance)

49. What type of medical insurance do you currently have? Please list all sources of coverage (for example, Medicare, Medicaid, private insurance, insurance through another family member, donation-related insurance).

_____

I have few questions about what you expect in the future. Here are some concerns that people sometimes have after donating an organ for transplantation. Please tell me tell me about whether you have any of these concerns.

50. How strongly do you agree or disagree with this statement: "Sometimes I worry that the liver donation will have negative effects on my health in the future." Would you say you… ☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree
51. How strongly do you agree or disagree with this statement: "Since my liver donation, I worry that I will never feel physically 100% well again." Would you say you… ☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree
52. How strongly do you agree or disagree with this statement: "Knowing what I know now, I would donate again." Would you say you… ☐ strongly agree ☐ agree ☐ are unsure ☐ disagree ☐ strongly disagree

54. How would you rate your overall feelings about your liver donation? Would you say they are…

☐ Very positive ☐ Somewhat positive ☐ A little positive ☐ Neither positive nor negative ☐ A little negative ☐ Very negative

59. Do you somehow feel like a better person after having donated a part of your liver?

☐ yes ☐ no

60. Here is a list of ways some people feel about liver donors. Tell me which is the closest to the way you would describe a living liver donor.

☐ anyone who donated part of their liver could be called a hero

☐ a person who donates part of their liver makes an exceptional sacrifice

☐ anyone who donates part of their liver makes a sacrifice somewhat out of the ordinary

☐ it is generous to give part of your liver but anyone should do as much

Lastly, I have few standard background questions.

56. How many people usually live in your home, <u>including</u> yourself? ___ people

57. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, <u>tell me to stop when I get to the right one</u>.

☐ $10,000 or less
☐ $20,000 or less
☐ $30,000 or less
☐ $40,000 or less
☐ $50,000 or less
☐ $60,000 or less
☐ $70,000 or less
☐ $80,000 or less
☐ $90,000 or less
☐ $100,000 or less
☐ $110,000 or less
☐ $120,000 or less
☐ $130,000 or less
☐ $140,000 or less
☐ $150,000 or less
☐ more than $150,000

58. Is there anything else that you think would be important for us to know about how you've been doing since the donation?

_____

_____

_____

Thank you!

We'll put your $20 payment in the mail and we'll be calling you back next year for an update on how you're doing.

Long-Term Follow-Up (Time 4)*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. We called you a year ago and I'm calling again today to update some information from last year. We want to learn about how you have been doing in the past year. I'll be asking you questions that are similar to those you answered last year. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all donors' answers in order to learn more about donors' well-being in the years after donation.

First, I have some questions about your opinions and feelings about the living donation process.

19. Looking back on the donation, in terms of the way you felt physically during and after the donation surgery, would you say that the donation was…

☐ very stressful ☐ pretty stressful ☐ not very stressful ☐ not at all stressful

20. Thinking about the liver transplant for which you donated, have you felt…

☐ very worthwhile ☐ a little worthwhile ☐ not at all worthwhile

21. When thinking about the liver transplant, have you felt…

☐ very proud ☐ a little proud ☐ not at all proud

22. When you think about the transplant, have you felt…

☐ very brave ☐ a little brave ☐ not at all brave

23. When you think about the transplant, have you felt…

☐ very heroic ☐ a little heroic ☐ not at all heroic

24. Since the transplant, would you say you think…

☐ more highly of yourself—that you're a better person than before the transplant

☐ less highly of yourself, or

☐ there is no change in the way you think of yourself

7. How often do you think about having donated a part of your liver? Would you say you think about it…

☐ More than once a day
☐ Once a day
☐ More than once a week
☐ Once a week
☐ Less often than once a week
☐ Never

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8. I'm going to read you some statements about the donation experience. On a scale where 1 indicates that the statement is not at all true and 10 indicates that the statement is very true, tell me how you feel about each statement.

Since the donation…	Not at all true										Very true
a. I feel better about myself.	0	1	2	3	4	5	6	7	8	9	10
b. My family has expressed gratitude to me.	0	1	2	3	4	5	6	7	8	9	10
c. My family seems to hold me in higher esteem.	0	1	2	3	4	5	6	7	8	9	10
d. I feel I have helped my recipient in a significant way.	0	1	2	3	4	5	6	7	8	9	10
e. I feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10
f. My family relationships feel more difficult.	0	1	2	3	4	5	6	7	8	9	10
g. My life has special meaning.	0	1	2	3	4	5	6	7	8	9	10

Now I have some questions about your health since the donation.

9. Physically, do you now feel completely back to normal?

☐ yes ☐ no

10. Are there specific physical activities that you can't do as well as before the surgery?

☐ Yes ☐ No

↳ What are they?_____

11. How often do you worry about the physical effects on you of having donated a part of your liver?

☐ often ☐ sometimes ☐ almost never

16. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

17. In the past year, have you developed any medical problems that you think are related to the donation surgery?

☐ Yes ☐ No

↳

please describe _____

14. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

25. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

26. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

27. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if your health now limits you a lot, limits you a little, or does not limit you at all in these activities.
[IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing several flights of stairs	_____	_____	_____
e.	Climbing one flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking more than a mile	_____	_____	_____
h.	Walking several hundred yards	_____	_____	_____
i.	Walking one hundred yards	_____	_____	_____
j.	Bathing or dressing yourself	_____	_____	_____

28. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

29. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

21. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

25. The next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

24. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)? Has it interfered…

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

25. Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

26. Here is a list of ways some people may feel physically after living organ donation. For each, please tell me if you have had the problem a lot, a little, or not at all <u>in the past month</u>.

	A LOT	A LITTLE	NOT AT ALL
a. Light headedness	1	2	3
b. Weakness	1	2	3
c. Tiredness	1	2	3
d. Bleeding at the site of the surgery	1	2	3
e. Pain at the site of the surgery	1	2	3
f. Itching at the site of the surgery	1	2	3

	A LOT	A LITTLE	NOT AT ALL
g. Tension around the site of the surgery	1	2	3
h. Numbness around the site of the surgery	1	2	3
i. Abdominal pain	1	2	3
j. Low back pain	1	2	3
k. Abdominal bloating or swelling	1	2	3
l. Decreased stomach tone	1	2	3
m. Puffiness in hands or feet	1	2	3
n. Leg swelling	1	2	3
o. Difficulty walking	1	2	3
p. Problems sleeping	1	2	3
q. Nausea or vomiting	1	2	3
r. Problems eating	1	2	3
s. Infection at the site of the surgery	1	2	3

27. I've asked you some general questions about pain. Now think about just the past 24 hours. In the **past 24 hours**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 28. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **past 24 hours**, pain has interfered with your:

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

28. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way <u>in the past week</u>.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

I'd like to turn now to how things have been with the transplant recipient and with other people.

31. First, what is your connection to the liver recipient? ***(RECORD WHETHER THE RECIPIENT IS THE DONOR'S SIBLING, PARENT, SPOUSE, FRIEND, ETC.)***:

    Recipient is _____

30. How often do you think about your liver recipient, on average? Would you say it is…

    □ More than once a day □ Two or three times a month
    □ Once a day □ Once a month
    □ More than once a week □ Less than once a month

31. Is your liver recipient currently: □ alive □ no longer alive, or □ you don't know

IF RECIPIENT IS NO LONGER ALIVE:

a. How long after the donation did your recipient die?_____

b. Have you sought counseling since the death of your recipient? □ yes □ no

c. Thinking about your recipient's death, please tell me about how you feel about the outcome: On a 10 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "10" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you rate how you feel about the outcome

Not at all guilty	1	2	3	4	5	6	7	8	9	10	very guilty
Not at all responsible	1	2	3	4	5	6	7	8	9	10	very responsible

IF RECIPIENT IS ALIVE:

d. How worried are you about your recipient?

□ very worried □ pretty worried □ not very worried □ not at all worried

e. How many times have you seen your recipient in the past year? _____ times

f. Would you like more contact or communication with your recipient?

□ yes, a lot more □ yes, a little more □ no

j. I'm going to read you some words that might describe your interactions with your liver recipient since the transplant. On a 7 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "7" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you describe your interactions with your liver recipient since the transplant?

Rewarding	1	2	3	4	5	6	7	Disappointing
Comfortable	1	2	3	4	5	6	7	Uncomfortable
Hard	1	2	3	4	5	6	7	Easy
Positive	1	2	3	4	5	6	7	Negative
Tense	1	2	3	4	5	6	7	Relaxed
Close	1	2	3	4	5	6	7	Distant
Awkward	1	2	3	4	5	6	7	Natural

h. Did your relationship with the recipient change after the transplant? Is your relationship with the recipient now…

□ much worse □ worse □ the same □ better □ much better

i. How would you rate the overall quality of your relationship with your recipient at this time? Would you say it is…

□ excellent □ very good □ average □ fair □ poor

j. Do you agree or disagree with this statement? "I feel closer to the recipient than I did before the transplant." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

n. Do you agree or disagree with this statement? "The recipient of my liver behaves in a way that risks the continued healthy functioning of the donated liver." Would you say you…

□ strongly agree □ agree □ neither agree nor disagree □ disagree □ strongly disagree

34. Compared to before the transplant, has your relationship with the rest of your family changed? Would you say it has…

□ Improved greatly
□ Improved somewhat
□ Stayed the same
□ Gotten somewhat worse

☐ Gotten much worse

46. What about any relationship you have with a spouse or partner. First, what is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

47. ***[IF PARTICIPANT IS MARRIED/ LIVING WITH PARTNER AND SPOUSE/PARTNER IS NOT THE TRANSPLANT RECIPIENT AS PER ITEM #29 ABOVE]:*** If you were married to or living with this person at the time of your donation, has your relationship with him/her changed, compared to before the transplant? Has it…

☐ Improved greatly
☐ Improved somewhat
☐ Stayed the same
☐ Gotten somewhat worse
☐ Gotten much worse
☐ Not applicable: was not married/living with this person at the time of the transplant

48. The next questions focus on how the donation experience may have affected you. I'm going to read you a list of ways people sometimes feel after having donated a part of their liver for transplantation. Please tell me if you agree a lot, agree a little, disagree a little or disagree a lot with each statement.

a. Being a liver donor makes a person feel that he/she is somehow a bigger and more worthwhile person. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
b. A person willing to donate part of their liver is almost a hero. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
c. Donating a part of my liver was really sort of a high point in my life, making everything seem more meaningful. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

49. Please tell me if you experienced any of the following as a result of the donation, where a zero means you did not experience it, up to a 5, meaning that you experienced it to a very great degree.

	Did not experience this					Experienced this to a very great degree
a. I changed my priorities about what is important in life.	0	1	2	3	4	5
b. I have a greater appreciation for the value of	0	1	2	3	4	5

	Did not experience this					Experienced this to a very great degree
my own life.						
c. I am able to do better things with my life.	0	1	2	3	4	5
d. I have a better understanding of spiritual matters.	0	1	2	3	4	5
e. I have a greater sense of closeness with others.	0	1	2	3	4	5
f. I established a new path for my life.	0	1	2	3	4	5
g. I know better that I can handle difficulties.	0	1	2	3	4	5
h. I have a stronger religious faith.	0	1	2	3	4	5
i. I discovered that I'm stronger than I thought I was.	0	1	2	3	4	5
j. I learned a great deal about how wonderful people are.	0	1	2	3	4	5

Now I'd like to focus on how you've been feeling recently.

37. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

40. Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Little interest or pleasure in doing things.	1	2	3	4
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

39. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 40. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

40. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 41.

Have any of the following happened to you more than once in the last 6 months?

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

The next questions are about how you have dealt with financial issues related to your liver donation.

41. First, are you currently employed (in a paid position)?

- ☐ Working full time
- ☐ Working part time by choice
- ☐ Working part time due to disease or illness
- ☐ Not working due to disease or illness
- ☐ Not working because you can't find a job
- ☐ Retired

42. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

49. Have you had to change jobs or modify your work <u>in the past year</u> because of your liver donation?

- ☐ No
- ☐ Yes, to a job with less manual labor
- ☐ Yes, to a less demanding or stressful job
- ☐ Yes, other changes: please describe:_____
- ☐ Not applicable because you have been unemployed for longer than the past year

50. <u>In the past year</u>, have you had any changes in your income because of your liver donation?

☐ No, it was not changed ☐ Yes, it decreased ☐ Yes, it increased

51. <u>In the past year</u>, have you had expenses related to your liver donation that were not covered by insurance? Tell me if you have had any of the following expenses due to the donation. ***(CHECK ALL THAT APPLY)***

- ☐ Lost wages
- ☐ Child or family members' care
- ☐ Transportation or parking costs
- ☐ Housing or lodging costs
- ☐ Food costs
- ☐ Medication costs not covered by any insurance
- ☐ Medical bills not covered by any insurance
- ☐ Other costs (list: _____)

46. Overall, across all of the years since donation, how have the costs related to the donation compared to what you expected?

☐ less than expected ☐ more than expected ☐ about what was expected

47. Overall, have the costs related to the donation been a significant financial burden for you?

☐ No, not a burden ☐ Yes, a mild burden ☐ Yes, a moderate burden ☐ Yes, a severe burden

50. <u>In the past year</u>, have you had any of the following insurance problems because of the donation?

g. Did you have trouble keeping the health insurance that you already had?

☐ no ☐ yes, I had trouble but was able to keep my insurance ☐ yes, I lost my health insurance as a result of the donation ☐ not applicable (did not have insurance)
h. Did you have trouble getting new health insurance because of the donation? ☐ no ☐ yes, I had trouble but was able to get new insurance ☐ yes, I was denied new health insurance ☐ not applicable (did not try to get new health insurance)
c. Did you have trouble keeping the life insurance you already had because of the donation? ☐ no ☐ yes, I had trouble but was able to keep my life insurance ☐ yes, I lost my life insurance ☐ not applicable (did not have life insurance)
d. Did you have trouble getting new life insurance because of the donation? ☐ no ☐ yes, I had trouble but was able to get new life insurance ☐ yes, I was denied new life insurance ☐ not applicable (did not try to get new life insurance)

49. What type of medical insurance do you currently have? Please list all sources of coverage (for example, Medicare, Medicaid, private insurance, insurance through another family member, donation-related insurance).

_____

I have few questions about what you expect in the future. Here are some concerns that people sometimes have after donating an organ for transplantation. Please tell me tell me about whether you have any of these concerns.

50. How strongly do you agree or disagree with this statement: "Sometimes I worry that the liver donation will have negative effects on my health in the future." Would you say you… ☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree
51. How strongly do you agree or disagree with this statement: "Since my liver donation, I worry that I will never feel physically 100% well again." Would you say you… ☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree
52. How strongly do you agree or disagree with this statement: "Knowing what I know now, I would donate again." Would you say you… ☐ strongly agree ☐ agree ☐ are unsure ☐ disagree ☐ strongly disagree

55. How would you rate your overall feelings about your liver donation? Would you say they are…

☐ Very positive ☐ Somewhat positive ☐ A little positive ☐ Neither positive nor negative ☐ A little negative ☐ Very negative

61. Do you somehow feel like a better person after having donated a part of your liver?

☐ yes ☐ no

62. Here is a list of ways some people feel about liver donors. Tell me which is the closest to the way you would describe a living liver donor.

☐ anyone who donated part of their liver could be called a hero

☐ a person who donates part of their liver makes an exceptional sacrifice

☐ anyone who donates part of their liver makes a sacrifice somewhat out of the ordinary

☐ it is generous to give part of your liver but anyone should do as much

Lastly, I have few standard background questions.

56. How many people usually live in your home, <u>including</u> yourself? ___ people

57. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, <u>tell me to stop when I get to the right one</u>.

☐ $10,000 or less
☐ $20,000 or less
☐ $30,000 or less
☐ $40,000 or less
☐ $50,000 or less
☐ $60,000 or less
☐ $70,000 or less
☐ $80,000 or less
☐ $90,000 or less
☐ $100,000 or less
☐ $110,000 or less
☐ $120,000 or less
☐ $130,000 or less
☐ $140,000 or less
☐ $150,000 or less
☐ more than $150,000

58. Is there anything else that you think would be important for us to know about how you've been doing since the donation?

_____

_____

_____

Thank you!

This is our final interview with you. We'll put your $20 payment in the mail.

Prospective Cohort Pre-Donation*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. Recently you agreed to be contacted by our survey research group for a telephone interview. We want to better understand the experiences of potential liver donors, as well as their health and well-being. This information will be used in order to help future potential donors as they go through the process of considering donation. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all study participants' answers in order to learn more about their views and their well-being.

First, I have some questions about how you came to be considering living donation.

25. Are there other possible donors for your liver transplant candidate?

    ☐ yes ☐ no

26. Which of the following statements best describes the <u>first</u> time you <u>ever</u> heard about living liver donation? Was it…

    ☐ before the liver transplant candidate got sick
    a. at the time the liver transplant candidate was first diagnosed
    b. some time after the liver transplant candidate was listed for transplantation
    c. at some other point (describe: _____)

27. Who first made it clear that you could be tested to donate part of your liver to your liver transplant candidate at this time? Tell me which statement is most accurate: Was it that…

    ☐ your liver transplant candidate first contacted you and made it clear that you could be tested to donate
    a. an employee of the medical center first contacted you
    b. another family member or friend contacted you (who? _____)
    c. you knew you could be tested to donate and you first contacted the medical center or your liver transplant candidate
    d. you heard about the possibility of donating to the candidate through the media (internet, television, newspaper, etc.)
    e. other (specify:_____)

28. When you first heard that your liver transplant candidate needed a liver donation, when did you decide to be tested to see if you could donate? Was it…

    ☐ immediately ☐ within a few months
    ☐ within a day ☐ within a year
    ☐ within a week ☐ more than a year
    ☐ within a month

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5. How hard was it for you to decide to donate? Would you say it was…

☐ very hard ☐ somewhat hard ☐ a little hard ☐ not at all hard to decide

6. Some liver donors have said that they postponed thinking about the big decision to donate, but just made the smaller decisions one step at a time – first deciding to undergo blood tests, then deciding to undergo a medical evaluation, and so on. Did you also postpone thinking about the big decision to actually donate a part of your liver?

☐ definitely ☐ sort of ☐ no

7. At what step in the procedure did you seriously consider donating a part of your liver to the transplant candidate? Was it…

☐ when you first learned about the disease the liver candidate has
☐ when you first learned the candidate might require a liver transplant
☐ when you were approached about being tested for donation
☐ when you learned you were medically cleared by the transplant team to donate
☐ other (specify:_____)

8. At what step in the procedure did you definitely decide you would be a liver donor? Was it…

☐ when you first learned about the disease the liver candidate has
☐ when you first learned the candidate might require a liver transplant
☐ when you were approached about being tested for donation
☐ when you learned you were medically cleared by the transplant team to donate
☐ other (specify:_____)

9. Would you say you…

☐ knew right away you would definitely be tested to be a liver donor when you first heard that your liver transplant candidate was in need, or

☐ you spent some time thinking it over

10. Did you consult anyone about your decision to become a liver donor, including… ***(CHECK ALL THAT APPLY)***

☐ the liver transplant candidate
☐ your spouse or partner
☐ your children
☐ other relatives
☐ friends
☐ other liver donors
☐ did not consult any of these people

11. Did you consult any professionals about your decision to become a liver donor, including… ***(CHECK ALL THAT APPLY)***

☐ my local doctor
☐ a lawyer

☐ medical personnel at the transplant center ☐ other (who:_____)
☐ a member of the clergy

12. Was there anyone who particularly wanted you to donate, or who encouraged you to do so?

☐ Yes ☐ No

→ Who encouraged you? ***(CHECK ALL THAT APPLY)***

☐ liver transplant candidate ☐ brother(s)
☐ spouse/partner ☐ other relatives
☐ mother ☐ friends
☐ father ☐ other (who:_____)
☐ sister(s)

13. Was there anyone who suggested any problems about donating or who tried to discourage you from donating?

☐ Yes ☐ No

→ Who discouraged you? ***(CHECK ALL THAT APPLY)***

☐ liver transplant candidate ☐ brother(s)
☐ spouse/partner ☐ other relatives
☐ mother ☐ friends
☐ father ☐ other (who:_____)
☐ sister(s)

14. Do you feel that your decision to donate was entirely voluntary?

☐ Yes ☐ No

→ At times, did you feel pressured to donate by: ***(CHECK ALL THAT APPLY)***

☐ liver transplant candidate
☐ friends
☐ family
☐ transplant team
☐ other (who:_____)

15. Many donors have doubts and worries about donating even though they go through with it. Have you ever had any doubts about donating?

☐ Yes ☐ No

I have a few questions about how you feel about donating at the present time.

16. How would you feel if you found out that you couldn't donate for some reason? Do you think you would

feel…

☐ very disappointed ☐ a little disappointed ☐ a little relieved ☐ very relieved

17. How much do you agree or disagree with this statement: "I sometimes feel unsure about donating." Do you…

☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

18. How much do you agree or disagree with this statement: "I sometimes hope the liver transplant candidate will end up getting a transplant from a deceased liver donor instead of me. Do you…

☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

19. How much do you agree or disagree with this statement: "I really want to donate myself even if someone else could do it." Do you…

☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

20. When you think about liver donation, do you feel…

☐ very brave ☐ a little brave ☐ not at all brave

21. How much do you agree or disagree with this statement: "A person willing to donate a part of their liver is almost a hero." Do you…

☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

The next set of questions focus on events in your past and present that may be related to you decision to become a liver donor.

22. While you were growing up, were either of your parents regular blood donors?

☐ Yes ☐ No ☐ Don't know

23. Has anyone in your family ever donated an organ for transplantation, such as a kidney?

☐ Yes ☐ No

↳ At the time of donation, was this family member…

☐ Alive ☐ No longer alive

24. Which of the following describes you? ***(CHECK ALL THAT APPLY)***

☐ Have you donated blood?
☐ Have you donated plasma?
☐ Are you in a bone marrow registry (such as the National Marrow Donor Program)?
☐ Have you donated bone marrow or stem cells?
☐ Have you signed an organ donor card (or listed "organ donor" on your driver's license)?

25. People help in different ways. Some people donate to charity, some do not. In the past year, have you donated funds to charity?

☐ Yes ☐ No

26. Are you currently active in any volunteer work?

☐ Yes ☐ No

How many hours per month do you do volunteer work? _____ hours per month

List the settings in which you have volunteered in the past year.

_____ _____

_____ _____

27. Regardless of whether or not you belong to a religion, tell me how important your religious beliefs are using a 7-point scale, where a 1 indicates that religious beliefs are not at all important or you have no religion, up to a 7 indicating that religious beliefs are extremely important or that your religious faith is the center of your life.

Not at all important. I have no religion.	1	2	3	4	5	6	7	Extremely important. My religious faith is the center of my life.

28. Donors have many reasons for deciding to donate a portion of their liver. We would like to know what your primary reasons are for donating. On a scale where 1 means "not at all true" and 7 means "very true," tell me how true each statement is about your reasons for donating.

	Not at all true						Very true
a. I am donating because I see myself as the kind of person who helps others.	1	2	3	4	5	6	7
b. I am donating because I was raised to believe that we should help others.	1	2	3	4	5	6	7
c. I am donating because life has been good to me, and I feel I should give something back in return.	1	2	3	4	5	6	7
d. I am donating because by helping others, I am helping to make this a better society in general.	1	2	3	4	5	6	7
e. I am donating because I felt it would be a good way to relieve the liver transplant candidate's suffering.	1	2	3	4	5	6	7
f. I am donating because I can imagine how it must feel to be waiting for a liver transplant.	1	2	3	4	5	6	7
g. I am donating because my religious beliefs suggest that I should help others.	1	2	3	4	5	6	7
h. I am donating because donating doesn't really cost me much.	1	2	3	4	5	6	7

	Not at all true						Very true
i. I am donating because it will help to raise awareness of the donation options so that donors might come forward if I ever need any type of transplant.	1	2	3	4	5	6	7
j. I am donating because I felt a moral obligation to donate.	1	2	3	4	5	6	7
k. I am donating because donating makes a truly significant contribution to the life of another.	1	2	3	4	5	6	7

I'd like to turn now to your relationship with the liver transplant candidate and your relationships with people in your family.

29. Tell me how well each of the following statements describe your relationship with the transplant candidate, where 1 means the statement is not at all accurate and 7 means it is very accurate.

	Not at all accurate						Very accurate
a. The liver transplant candidate and I see eye to eye on most issues.	1	2	3	4	5	6	7
b. The liver transplant candidate and I have had frequent heated conflicts over the years.	1	2	3	4	5	6	7
c. I would describe my relationship with the liver transplant candidate as warm and close.	1	2	3	4	5	6	7
d. I generally enjoy the company of the liver transplant candidate.	1	2	3	4	5	6	7

Now think about people in your family (in addition to the transplant candidate, if that person is a family member).

30. Do you think your parents (and brothers and sisters) during the recent years have been…

- ☐ Generally approving and accepting of you and your life, or
- ☐ Not generally approving, or
- ☐ You don't know

31. Have you done anything major in your life that you family didn't approve of?

☐ Yes ☐ No

32. How strongly do you agree or disagree with the following statement: "My spouse (or partner) supports my decision to donate a part of my liver." Do you…

☐ Strongly agree ☐ Agree ☐ Disagree ☐ Strongly disagree ☐ Not applicable (no spouse/partner)

33. How strongly do you agree or disagree with the following statement: "My parents support my decision to donate a part of my liver." Do you…

☐ Strongly agree ☐ Agree ☐ Disagree ☐ Strongly disagree ☐ Not applicable

Now I have some questions about your general health and well-being.

34. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

35. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

36. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

37. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if <u>your health now</u> limits you a lot, limits you a little, or does not limit you at all in these activities.
IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing <u>several</u> flights of stairs	_____	_____	_____
e.	Climbing <u>one</u> flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking <u>more than a mile</u>	_____	_____	_____
h.	Walking <u>several hundred yards</u> (CHECK)	_____	_____	_____
i.	Walking <u>one hundred yards</u>	_____	_____	_____
j.	Bathing or dressing yourself	_____	_____	_____

38. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

39. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

40. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

41. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

42. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

43. The next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

44. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

45. Now, I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

46. I've asked you a few general questions about pain. Now think about just the past 24 hours. In the **<u>past 24 hours</u>**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0 1 2 3 4 5 6 7 8 9 10

NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 47. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **<u>past 24 hours</u>**, pain has interfered with your:

Does not interfere	Completely interferes

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

47. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way <u>in the past week</u>.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

48. Now think about your health in general. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

49. Some people who are going to become liver donors have concerns about the <u>medical procedure</u>. Here is a list of concerns that a potential liver donor might have. Please tell me whether you <u>ever had</u> any of these concerns about donating. ***[CHECK ALL THAT APPLY]***

- ☐ Concerns that the surgery might be painful
- ☐ Concerns about undergoing general anesthesia
- ☐ Concerns that the surgery might damage your health
- ☐ Concerns that your recovery might be difficult
- ☐ Other medical concerns (what?_____)
- ☐ None; you have never had medical concerns

50. Do you think it is possible that a liver donor could experience a serious medical complication from donating?

☐ Yes ☐ No

51. Some people who are going to become liver donors have concerns about work, family, or financial issues. Please tell me whether you <u>ever had</u> any of these concerns about donating. ***[CHECK ALL THAT APPLY]***

- ☐ Concerns about missing time from work for the donation
- ☐ Concerns about missing important family activities
- ☐ Concerns about who would take care of my children
- ☐ Concerns that my family would worry about me
- ☐ Concerns about what friends or other relatives would think
- ☐ Concerns about who would pay for the procedure
- ☐ Other concerns (what?_____)
- ☐ None; you have never had work, family or financial concerns

52. Do you think that donating a portion of your liver will have any long-term effects on your health?

☐ Definitely ☐ Probably ☐ Maybe ☐ No, no long-term effects

Now I'd like to change to a different topic and focus on how you've been feeling recently.

53. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

54. Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Little interest or pleasure in doing things.	1	2	3	4

	Not At All	Several Days	More Than Half The Days	Nearly Every Day
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

55. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not At All	Several Days	More Than Half The Days	Nearly Every Day
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 56. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

56. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 57.

Have any of the following happened to you more than once in the last 6 months?

	Yes	No

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

57. I have few questions about what you expect in the future. Please tell me how likely each of the following events is, where 1 means an event is very unlikely and 10 means it is very likely.

	Very unlikely										Very likely
a. You will actually donate a part of your liver.	0	1	2	3	4	5	6	7	8	9	10
b. The liver transplant candidate will survive the transplant.	0	1	2	3	4	5	6	7	8	9	10
c. The liver transplant candidate will return to a full and active life after the transplant.	0	1	2	3	4	5	6	7	8	9	10

58. Imagine that you have <u>already donated</u>. Tell me how likely each of the following statements is, where 1 is very unlikely and 10 is very likely

	Very unlikely										Very likely
a. I will have relieved the liver recipient's suffering.	0	1	2	3	4	5	6	7	8	9	10
b. I will feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10

59. How many days do you think you will be in the hospital following the donation? _____ days

60. If you are employed, how long do you think you will be off work? _____ days

61. How long do you think it will be before you feel back to normal?

☐ Less than 1 month ☐ 1 -3 months ☐ Greater than 3 months

62. Do you feel well prepared for the donation experience?

☐ Yes, totally ☐ Yes, but could be better prepared ☐ no

Lastly, I have few standard background questions.

63. How far did you go in school?
☐ grammar school (grades 1 - 6)
☐ junior high school (through 9th grade)
☐ some high school (grades 10 - 11)
☐ high school graduate
☐ vocational school or some college
☐ college graduate
☐ some graduate school
☐ graduate or professional degree

64. Are you currently employed (in a paid position)?

☐ Working full time
☐ Working part time by choice
☐ Working part time due to disease or illness
☐ Not working due to disease or illness
☐ Not working because you can't find a job
☐ Retired

65. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

66. What is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

67. How many people usually live in your home, <u>including</u> yourself? ___ people

68. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, <u>tell me to stop when I get to the right one</u>.

☐ $10,000 or less
☐ $20,000 or less
☐ $30,000 or less
☐ $40,000 or less
☐ $70,000 or less
☐ $80,000 or less
☐ $90,000 or less
☐ $100,000 or less
☐ $130,000 or less
☐ $140,000 or less
☐ $150,000 or less
☐ more than $150,000

- ☐ $50,000 or less
- ☐ $60,000 or less
- ☐ $110,000 or less
- ☐ $120,000 or less

69. Is there anything else that you think would be important for us to know about in order to help future potential donors?

_____

_____

_____

Thank you!

We'll put your $20 payment in the mail and we'll be calling you back at about 3 months after your liver donation surgery for an update on how you're doing.

Prospective Cohort 3 Months Post-Donation*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. We called you shortly before your liver donation and I'm calling again today since it has been about 3 months since the donation. We want to learn about how you have been doing since the donation surgery. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all donors' answers in order to learn more about donors' well-being in the years after donation.

First, I have some questions about your opinions and feelings about the living donation process.

29. Looking back on the donation, in terms of the way you felt physically during and after the donation surgery, would you say that the donation was…

☐ very stressful ☐ pretty stressful ☐ not very stressful ☐ not at all stressful

30. Thinking about the liver transplant for which you donated, have you felt…

☐ very worthwhile ☐ a little worthwhile ☐ not at all worthwhile

31. When thinking about the liver transplant, have you felt…

☐ very proud ☐ a little proud ☐ not at all proud

32. When you think about the transplant, have you felt…

☐ very brave ☐ a little brave ☐ not at all brave

33. When you think about the transplant, have you felt…

☐ very heroic ☐ a little heroic ☐ not at all heroic

34. Since the transplant, would you say you think…

☐ more highly of yourself—that you're a better person than before the transplant

☐ less highly of yourself, or

☐ there is no change in the way you think of yourself

7. How often do you think about having donated a part of your liver? Would you say you think about it…

☐ More than once a day ☐ Once a week
☐ Once a day ☐ Less often than once a week
☐ More than once a week ☐ Never

***Most items in this survey are copyrighted by scale authors and are used with permission.**

8. I'm going to read you some statements about the donation experience. On a scale where 1 indicates that the statement is not at all true and 10 indicates that the statement is very true, tell me how you feel about each statement.

Since the donation…	Not at all true										Very true
a. I feel better about myself.	0	1	2	3	4	5	6	7	8	9	10
b. My family has expressed gratitude to me.	0	1	2	3	4	5	6	7	8	9	10
c. My family seems to hold me in higher esteem.	0	1	2	3	4	5	6	7	8	9	10
d. I feel I have helped my recipient in a significant way.	0	1	2	3	4	5	6	7	8	9	10
e. I feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10
f. My family relationships feel more difficult.	0	1	2	3	4	5	6	7	8	9	10
g. My life has special meaning.	0	1	2	3	4	5	6	7	8	9	10

Now I have some questions about your health since the donation.

9. Physically, how long did it take after the liver donation surgery before you felt completely back to normal? Would you say it took…

- ☐ 1 week
- ☐ 2 to 3 weeks
- ☐ 4 to 5 weeks
- ☐ 6 to 7 weeks
- ☐ 2 months
- ☐ you still do not feel back to normal

11. Compared to what you expected, would you say that your recovery was slower or faster than expected? Would you say it was…

☐ much slower than expected ☐ slower ☐ as expected ☐ faster ☐ much faster

11. Are there specific physical activities that you can't do as well as before the surgery?

☐ Yes ☐ No

↳ What are they?_____

12. How often do you worry about the physical effects on you of having donated a part of your liver?

☐ Often ☐ sometimes ☐ almost never

15. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

16. Since the donation, have you developed any medical problems that you think are related to the donation surgery?

☐ Yes ☐ No

→ please describe _____

15. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

21. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

22. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

23. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if <u>your health now</u> limits you a lot, limits you a little, or does not limit you at all in these activities.
[IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing <u>several</u> flights of stairs	_____	_____	_____
e.	Climbing <u>one</u> flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking <u>more than a mile</u>	_____	_____	_____
h.	Walking <u>several hundred yards</u>	_____	_____	_____

i. Walking one hundred yards	_____	_____	_____
j. Bathing or dressing yourself	_____	_____	_____

24. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

25. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

21. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

22. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

23. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

25. The next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

25. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? Has it interfered…

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

26. Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

27. Here is a list of ways some people may feel physically after living organ donation. For each, please tell me if you have had the problem a lot, a little, or not at all in the past month.

	A LOT	A LITTLE	NOT AT ALL

	A LOT	A LITTLE	NOT AT ALL
a. Light headedness	1	2	3
b. Weakness	1	2	3
c. Tiredness	1	2	3
d. Bleeding at the site of the surgery	1	2	3
e. Pain at the site of the surgery	1	2	3
f. Itching at the site of the surgery	1	2	3
g. Tension around the site of the surgery	1	2	3
h. Numbness around the site of the surgery	1	2	3
i. Abdominal pain	1	2	3
j. Low back pain	1	2	3
k. Abdominal bloating or swelling	1	2	3
l. Decreased stomach tone	1	2	3
m. Puffiness in hands or feet	1	2	3
n. Leg swelling	1	2	3
o. Difficulty walking	1	2	3
p. Problems sleeping	1	2	3
q. Nausea or vomiting	1	2	3
r. Problems eating	1	2	3
s. Infection at the site of the surgery	1	2	3

28. I've asked you some general questions about pain. Now think about just the past 24 hours. In the **past 24 hours**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 29. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **past 24 hours**, pain has interfered with your:

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

29. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way in the past week.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

I'd like to turn now to how things have been with the transplant recipient and with other people.

31. First, what is your connection to the liver recipient? ***(RECORD WHETHER THE RECIPIENT IS THE DONOR'S SIBLING, PARENT, SPOUSE, FRIEND, ETC.)***:

Recipient is _____

31. How often do you think about your liver recipient, on average? Would you say it is…

☐ More than once a day ☐ Two or three times a month
☐ Once a day ☐ Once a month
☐ More than once a week ☐ Less than once a month

32. Is your liver recipient currently: ☐ alive ☐ no longer alive, or ☐ you don't know

IF RECIPIENT IS NO LONGER ALIVE:

a. How long after the donation did your recipient die?_____

b. Have you sought counseling since the death of your recipient? ☐ yes ☐ no

c. Thinking about your recipient's death, please tell me about how you feel about the outcome: On a 10 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "10" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you rate how you feel about the outcome

Not at all guilty 1 2 3 4 5 6 7 8 9 10 very guilty

IF RECIPIENT IS ALIVE:

d. How worried are you about your recipient?

□ very worried □ pretty worried □ not very worried □ not at all worried

e. How many times have you seen your recipient in the past year? _____ times

f. Would you like more contact or communication with your recipient?

□ yes, a lot more □ yes, a little more □ no

k. I'm going to read you some words that might describe your interactions with your liver recipient since the transplant. On a 7 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "7" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you describe your interactions with your liver recipient since the transplant?

Rewarding	1	2	3	4	5	6	7	Disappointing
Comfortable	1	2	3	4	5	6	7	Uncomfortable
Hard	1	2	3	4	5	6	7	Easy
Positive	1	2	3	4	5	6	7	Negative
Tense	1	2	3	4	5	6	7	Relaxed
Close	1	2	3	4	5	6	7	Distant
Awkward	1	2	3	4	5	6	7	Natural

h. Did your relationship with the recipient change after the transplant? Is your relationship with the recipient now…

□ much worse □ worse □ the same □ better □ much better

i. How would you rate the overall quality of your relationship with your recipient at this time? Would you say it is…

□ excellent □ very good □ average □ fair □ poor

j. Do you agree or disagree with this statement? "I feel closer to the recipient than I did before the transplant." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

o. Do you agree or disagree with this statement? "The recipient of my liver behaves in a way that risks the continued healthy functioning of the donated liver." Would you say you…

□ strongly agree □ agree □ neither agree nor disagree □ disagree □ strongly disagree

50. Compared to before the transplant, has your relationship with the rest of your family changed? Would you say it has…

□ Improved greatly

- ☐ Improved somewhat
- ☐ Stayed the same
- ☐ Gotten somewhat worse
- ☐ Gotten much worse

51. What about any relationship you have with a spouse or partner. First, what is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

52. ***[IF PARTICIPANT IS MARRIED/ LIVING WITH PARTNER AND SPOUSE/PARTNER IS NOT THE TRANSPLANT RECIPIENT AS PER ITEM #30 ABOVE]:*** If you were married to or living with this person at the time of your donation, has your relationship with him/her changed, compared to before the transplant? Has it…

- ☐ Improved greatly
- ☐ Improved somewhat
- ☐ Stayed the same
- ☐ Gotten somewhat worse
- ☐ Gotten much worse
- ☐ Not applicable: was not married/living with this person at the time of the transplant

53. The next questions focus on how the donation experience may have affected you. I'm going to read you a list of ways people sometimes feel after having donated a part of their liver for transplantation. Please tell me if you agree a lot, agree a little, disagree a little or disagree a lot with each statement.

a. Being a liver donor makes a person feel that he/she is somehow a bigger and more worthwhile person. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
b. A person willing to donate part of their liver is almost a hero. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
c. Donating a part of my liver was really sort of a high point in my life, making everything seem more meaningful. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

Now I'd like to focus on how you've been feeling recently.

37. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

38. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not At All	Several Days	More Than Half The Days	Nearly Every Day
a. Little interest or pleasure in doing things.	1	2	3	4
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

39. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not At All	Several Days	More Than Half The Days	Nearly Every Day
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 40. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

40. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 41.

Have any of the following happened to you more than once in the last 6 months?

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

The next questions are about how you have dealt with financial issues related to your liver donation.

41. First, are you currently employed (in a paid position)?

- ☐ Working full time
- ☐ Working part time by choice
- ☐ Working part time due to disease or illness
- ☐ Not working due to disease or illness
- ☐ Not working because you can't find a job
- ☐ Retired

42. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

43. Have you had to change jobs or modify your work because of your liver donation?

- ☐ No
- ☐ Yes, to a job with less manual labor
- ☐ Yes, to a less demanding or stressful job
- ☐ Yes, other changes: please describe:_____
- ☐ Not applicable because not employed before donation

44. Have you had any changes in your income because of your liver donation?

☐ No, it has not changed ☐ Yes, it decreased ☐ Yes, it increased

45. Have you had expenses related to your liver donation that were not covered by insurance? Tell me if you have had any of the following expenses due to the donation. ***(CHECK ALL THAT APPLY)***

☐ Lost wages
☐ Child or family members' care
☐ Transportation or parking costs
☐ Housing or lodging costs
☐ Food costs
☐ Medication costs not covered by any insurance
☐ Medical bills not covered by any insurance
☐ Other costs (list: _____)

46. Overall, how have the costs related to the donation compared to what you expected?

☐ less than expected ☐ more than expected ☐ about what was expected

47. Overall, have the costs related to the donation been a significant financial burden for you?

☐ No, not a burden ☐ Yes, a mild burden ☐ Yes, a moderate burden ☐ Yes, a severe burden

48. Have you had any of the following insurance problems because of the donation?

i. Did you have trouble keeping the health insurance that you already had? ☐ no ☐ yes, I had trouble but was able to keep my insurance ☐ yes, I lost my health insurance as a result of the donation ☐ not applicable (did not have insurance)
j. Did you have trouble getting new health insurance because of the donation? ☐ no ☐ yes, I had trouble but was able to get new insurance ☐ yes, I was denied new health insurance ☐ not applicable (did not try to get new health insurance)
c. Did you have trouble keeping the life insurance you already had because of the donation? ☐ no ☐ yes, I had trouble but was able to keep my life insurance ☐ yes, I lost my life insurance ☐ not applicable (did not have life insurance)
d. Did you have trouble getting new life insurance because of the donation? ☐ no ☐ yes, I had trouble but was able to get new life insurance ☐ yes, I was denied new life insurance ☐ not applicable (did not try to get new life insurance)

49. What type of medical insurance do you currently have? Please list all sources of coverage (for example, Medicare, Medicaid, private insurance, insurance through another family member, donation-related insurance).

_____

I have few questions about what you expect in the future. Here are some concerns that people sometimes have after donating an organ for transplantation. Please tell me tell me about whether you have any of these concerns.

50. How strongly do you agree or disagree with this statement: "Sometimes I worry that the liver donation will have negative effects on my health in the future." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

51. How strongly do you agree or disagree with this statement: "Since my liver donation, I worry that I will never feel physically 100% well again." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

52. How strongly do you agree or disagree with this statement: "Knowing what I know now, I would donate again." Would you say you…

☐ strongly agree ☐ agree ☐ are unsure ☐ disagree ☐ strongly disagree

53. How would you rate your overall feelings about your liver donation? Would you say they are…

☐ Very positive ☐ Somewhat positive ☐ A little positive ☐ Neither positive nor negative ☐ A little negative ☐ Very negative

54. Do you somehow feel like a better person after having donated a part of your liver?

☐ yes ☐ no

55. Here is a list of ways some people feel about liver donors. Tell me which is the closest to the way you would describe a living liver donor.

☐ anyone who donated part of their liver could be called a hero

☐ a person who donates part of their liver makes an exceptional sacrifice

☐ anyone who donates part of their liver makes a sacrifice somewhat out of the ordinary

☐ it is generous to give part of your liver but anyone should do as much

Lastly, I have few standard background questions.

56. How many people usually live in your home, including yourself? ___ people

57. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, tell me to stop when I get to the right one.

☐ $10,000 or less	☐ $70,000 or less	☐ $130,000 or less
☐ $20,000 or less	☐ $80,000 or less	☐ $140,000 or less
☐ $30,000 or less	☐ $90,000 or less	☐ $150,000 or less
☐ $40,000 or less	☐ $100,000 or less	☐ more than $150,000
☐ $50,000 or less	☐ $110,000 or less	
☐ $60,000 or less	☐ $120,000 or less	

58. Is there anything else that you think would be important for us to know about how you've been doing since the donation?

_____

_____

_____

Thank you!

We'll put your $20 payment in the mail and we'll be calling you back in about 3 months for an update on how you're doing.

Prospective Cohort 6 Months Post-Donation*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. We called you 3 months ago and I'm calling again today to update some information since then. We want to learn about how you have been doing recently. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all donors' answers in order to learn more about donors' well-being in the years after donation.

First, I have some questions about your opinions and feelings about the living donation process.

35. Looking back on the donation, in terms of the way you felt physically during and after the donation surgery, would you say that the donation was…

☐ very stressful ☐ pretty stressful ☐ not very stressful ☐ not at all stressful

36. Thinking about the liver transplant for which you donated, have you felt…

☐ very worthwhile ☐ a little worthwhile ☐ not at all worthwhile

37. When thinking about the liver transplant, have you felt…

☐ very proud ☐ a little proud ☐ not at all proud

38. When you think about the transplant, have you felt…

☐ very brave ☐ a little brave ☐ not at all brave

39. When you think about the transplant, have you felt…

☐ very heroic ☐ a little heroic ☐ not at all heroic

40. Since the transplant, would you say you think…

☐ more highly of yourself—that you're a better person than before the transplant

☐ less highly of yourself, or

☐ there is no change in the way you think of yourself

7. How often do you think about having donated a part of your liver? Would you say you think about it…

☐ More than once a day ☐ Once a week
☐ Once a day ☐ Less often than once a week
☐ More than once a week ☐ Never

8. I'm going to read you some statements about the donation experience. On a scale where 1 indicates that the statement is not at all true and 10 indicates that the statement is very true, tell me how you feel about each statement.

Since the donation…	Not at all true										Very true
a. I feel better about myself.	0	1	2	3	4	5	6	7	8	9	10
b. My family has expressed gratitude to me.	0	1	2	3	4	5	6	7	8	9	10
c. My family seems to hold me in higher esteem.	0	1	2	3	4	5	6	7	8	9	10
d. I feel I have helped my recipient in a significant way.	0	1	2	3	4	5	6	7	8	9	10
e. I feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10
f. My family relationships feel more difficult.	0	1	2	3	4	5	6	7	8	9	10
g. My life has special meaning.	0	1	2	3	4	5	6	7	8	9	10

Now I have some questions about your health since the donation.

9. Physically, how long did it take after the liver donation surgery before you felt completely back to normal? Would you say it took…

☐ 1 week
☐ 2 to 3 weeks
☐ 4 to 5 weeks
☐ 6 to 7 weeks
☐ 2 months
☐ 3 months
☐ 4 months
☐ 5 months
☐ you still do not feel back to normal

12. Compared to what you expected, would you say that your recovery was slower or faster than expected? Would you say it was…

☐ much slower than expected ☐ slower ☐ as expected ☐ faster ☐ much faster

11. Are there specific physical activities that you can't do as well as before the surgery?

☐ Yes ☐ No

↳ What are they?_____

12. How often do you worry about the physical effects on you of having donated a part of your liver?

☐ often ☐ sometimes ☐ almost never

17. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

18. Since the donation, have you developed any medical problems that you think are related to the donation surgery?

☐ Yes ☐ No

→ please describe _____

15. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

26. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

27. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

28. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if <u>your health now</u> limits you a lot, limits you a little, or does not limit you at all in these activities.
[IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing <u>several</u> flights of stairs	_____	_____	_____
e.	Climbing <u>one</u> flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking <u>more than a mile</u>	_____	_____	_____
h.	Walking <u>several hundred yards</u>	_____	_____	_____

i. Walking one hundred yards	_____	_____	_____
j. Bathing or dressing yourself	_____	_____	_____

29. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

30. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

21. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

22. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

23. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

26. The next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

25. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? Has it interfered…

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

26. Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

27. Here is a list of ways some people may feel physically after living organ donation. For each, please tell me if you have had the problem a lot, a little, or not at all in the past month.

	A LOT	A LITTLE	NOT AT ALL

	A LOT	A LITTLE	NOT AT ALL
a. Light headedness	1	2	3
b. Weakness	1	2	3
c. Tiredness	1	2	3
d. Bleeding at the site of the surgery	1	2	3
e. Pain at the site of the surgery	1	2	3
f. Itching at the site of the surgery	1	2	3
g. Tension around the site of the surgery	1	2	3
h. Numbness around the site of the surgery	1	2	3
i. Abdominal pain	1	2	3
j. Low back pain	1	2	3
k. Abdominal bloating or swelling	1	2	3
l. Decreased stomach tone	1	2	3
m. Puffiness in hands or feet	1	2	3
n. Leg swelling	1	2	3
o. Difficulty walking	1	2	3
p. Problems sleeping	1	2	3
q. Nausea or vomiting	1	2	3
r. Problems eating	1	2	3
s. Infection at the site of the surgery	1	2	3

28. I've asked you some general questions about pain. Now think about just the past 24 hours. In the **past 24 hours**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 29. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **past 24 hours**, pain has interfered with your:

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

29. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way in the past week.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

I'd like to turn now to how things have been with the transplant recipient and with other people.

32. First, what is your connection to the liver recipient? ***(RECORD WHETHER THE RECIPIENT IS THE DONOR'S SIBLING, PARENT, SPOUSE, FRIEND, ETC.)***:

Recipient is _____

31. How often do you think about your liver recipient, on average? Would you say it is…

☐ More than once a day ☐ Two or three times a month
☐ Once a day ☐ Once a month
☐ More than once a week ☐ Less than once a month

32. Is your liver recipient currently: ☐ alive ☐ no longer alive, or ☐ you don't know

IF RECIPIENT IS NO LONGER ALIVE:

a. How long after the donation did your recipient die?_____

b. Have you sought counseling since the death of your recipient? ☐ yes ☐ no

c. Thinking about your recipient's death, please tell me about how you feel about the outcome: On a 10 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "10" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you rate how you feel about the outcome

Not at all guilty 1 2 3 4 5 6 7 8 9 10 very guilty

IF RECIPIENT IS ALIVE:

d. How worried are you about your recipient?

□ very worried □ pretty worried □ not very worried □ not at all worried

e. How many times have you seen your recipient in the past year? _____ times

f. Would you like more contact or communication with your recipient?

□ yes, a lot more □ yes, a little more □ no

l. I'm going to read you some words that might describe your interactions with your liver recipient since the transplant. On a 7 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "7" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you describe your interactions with your liver recipient since the transplant?

Rewarding	1	2	3	4	5	6	7	Disappointing
Comfortable	1	2	3	4	5	6	7	Uncomfortable
Hard	1	2	3	4	5	6	7	Easy
Positive	1	2	3	4	5	6	7	Negative
Tense	1	2	3	4	5	6	7	Relaxed
Close	1	2	3	4	5	6	7	Distant
Awkward	1	2	3	4	5	6	7	Natural

h. Did your relationship with the recipient change after the transplant? Is your relationship with the recipient now…

□ much worse □ worse □ the same □ better □ much better

i. How would you rate the overall quality of your relationship with your recipient at this time? Would you say it is…

□ excellent □ very good □ average □ fair □ poor

j. Do you agree or disagree with this statement? "I feel closer to the recipient than I did before the transplant." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

p. Do you agree or disagree with this statement? "The recipient of my liver behaves in a way that risks the continued healthy functioning of the donated liver." Would you say you…

□ strongly agree □ agree □ neither agree nor disagree □ disagree □ strongly disagree

54. Compared to before the transplant, has your relationship with the rest of your family changed? Would you say it has…

□ Improved greatly

- ☐ Improved somewhat
- ☐ Stayed the same
- ☐ Gotten somewhat worse
- ☐ Gotten much worse

55. What about any relationship you have with a spouse or partner. First, what is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

56. ***[IF PARTICIPANT IS MARRIED/ LIVING WITH PARTNER AND SPOUSE/PARTNER IS NOT THE TRANSPLANT RECIPIENT AS PER ITEM #30 ABOVE]:*** If you were married to or living with this person at the time of your donation, has your relationship with him/her changed, compared to before the transplant? Has it…

- ☐ Improved greatly
- ☐ Improved somewhat
- ☐ Stayed the same
- ☐ Gotten somewhat worse
- ☐ Gotten much worse
- ☐ Not applicable: was not married/living with this person at the time of the transplant

57. The next questions focus on how the donation experience may have affected you. I'm going to read you a list of ways people sometimes feel after having donated a part of their liver for transplantation. Please tell me if you agree a lot, agree a little, disagree a little or disagree a lot with each statement.

a. Being a liver donor makes a person feel that he/she is somehow a bigger and more worthwhile person. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
b. A person willing to donate part of their liver is almost a hero. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
c. Donating a part of my liver was really sort of a high point in my life, making everything seem more meaningful. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

Now I'd like to focus on how you've been feeling recently.

37. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

39. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not At All	Several Days	More Than Half The Days	Nearly Every Day
a. Little interest or pleasure in doing things.	1	2	3	4
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

39. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not At All	Several Days	More Than Half The Days	Nearly Every Day
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 40. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

40. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 41.

Have any of the following happened to you more than once in the last 6 months?

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

The next questions are about how you have dealt with financial issues related to your liver donation.

41. First, are you currently employed (in a paid position)?

- ☐ Working full time
- ☐ Working part time by choice
- ☐ Working part time due to disease or illness
- ☐ Not working due to disease or illness
- ☐ Not working because you can't find a job
- ☐ Retired

42. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

46. Since we last spoke with you, have you had to change jobs or modify your work because of your liver donation?

- ☐ No
- ☐ Yes, to a job with less manual labor
- ☐ Yes, to a less demanding or stressful job
- ☐ Yes, other changes: please describe:_____
- ☐ Not applicable because not employed before donation

47. Since we last spoke with you, have you had any changes in your income because of your liver donation?

☐ No, it has not changed ☐ Yes, it decreased ☐ Yes, it increased

48. Since we last spoke with you, have you had expenses related to your liver donation that were not covered by insurance? Tell me if you have had any of the following expenses due to the donation. ***(CHECK ALL THAT APPLY)***

☐ Lost wages
☐ Child or family members' care
☐ Transportation or parking costs
☐ Housing or lodging costs
☐ Food costs
☐ Medication costs not covered by any insurance
☐ Medical bills not covered by any insurance
☐ Other costs (list: _____)

46. Overall, how have the costs related to the donation compared to what you expected?

☐ less than expected ☐ more than expected ☐ about what was expected

47. Overall, have the costs related to the donation been a significant financial burden for you?

☐ No, not a burden ☐ Yes, a mild burden ☐ Yes, a moderate burden ☐ Yes, a severe burden

49. Since we last spoke with you, have you had any of the following insurance problems because of the donation?

k. Did you have trouble keeping the health insurance that you already had? ☐ no ☐ yes, I had trouble but was able to keep my insurance ☐ yes, I lost my health insurance as a result of the donation ☐ not applicable (did not have insurance)
l. Did you have trouble getting new health insurance because of the donation? ☐ no ☐ yes, I had trouble but was able to get new insurance ☐ yes, I was denied new health insurance ☐ not applicable (did not try to get new health insurance)
c. Did you have trouble keeping the life insurance you already had because of the donation? ☐ no ☐ yes, I had trouble but was able to keep my life insurance ☐ yes, I lost my life insurance ☐ not applicable (did not have life insurance)
d. Did you have trouble getting new life insurance because of the donation? ☐ no ☐ yes, I had trouble but was able to get new life insurance ☐ yes, I was denied new life insurance ☐ not applicable (did not try to get new life insurance)

49. What type of medical insurance do you currently have? Please list all sources of coverage (for example, Medicare, Medicaid, private insurance, insurance through another family member, donation-related insurance).

_____

I have few questions about what you expect in the future. Here are some concerns that people sometimes have after donating an organ for transplantation. Please tell me tell me about whether you have any of these concerns.

50. How strongly do you agree or disagree with this statement: "Sometimes I worry that the liver donation will have negative effects on my health in the future." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

51. How strongly do you agree or disagree with this statement: "Since my liver donation, I worry that I will never feel physically 100% well again." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree

52. How strongly do you agree or disagree with this statement: "Knowing what I know now, I would donate again." Would you say you…

☐ strongly agree ☐ agree ☐ are unsure ☐ disagree ☐ strongly disagree

56. How would you rate your overall feelings about your liver donation? Would you say they are…

☐ Very positive ☐ Somewhat positive ☐ A little positive ☐ Neither positive nor negative ☐ A little negative ☐ Very negative

57. Do you somehow feel like a better person after having donated a part of your liver?

☐ yes ☐ no

58. Here is a list of ways some people feel about liver donors. Tell me which is the closest to the way you would describe a living liver donor.

☐ anyone who donated part of their liver could be called a hero

☐ a person who donates part of their liver makes an exceptional sacrifice

☐ anyone who donates part of their liver makes a sacrifice somewhat out of the ordinary

☐ it is generous to give part of your liver but anyone should do as much

Lastly, I have few standard background questions.

56. How many people usually live in your home, including yourself? ___ people

57. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, tell me to stop when I get to the right one.

☐ $10,000 or less	☐ $70,000 or less	☐ $130,000 or less
☐ $20,000 or less	☐ $80,000 or less	☐ $140,000 or less
☐ $30,000 or less	☐ $90,000 or less	☐ $150,000 or less
☐ $40,000 or less	☐ $100,000 or less	☐ more than $150,000
☐ $50,000 or less	☐ $110,000 or less	
☐ $60,000 or less	☐ $120,000 or less	

58. Is there anything else that you think would be important for us to know about how you've been doing since the donation?

_____

_____

_____

Thank you!

We'll put your $20 payment in the mail and we'll be calling you back in about 6 months for an update on how you're doing.

Prospective Cohort 1 Year Post-Donation*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. We called you 6 months ago and I'm calling again today to update some information since then. We want to learn about how you have been doing recently. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all donors' answers in order to learn more about donors' well-being in the years after donation.

First, I have some questions about your opinions and feelings about the living donation process.

41. Looking back on the donation, in terms of the way you felt physically during and after the donation surgery, would you say that the donation was…

☐ very stressful ☐ pretty stressful ☐ not very stressful ☐ not at all stressful

42. Thinking about the liver transplant for which you donated, have you felt…

☐ very worthwhile ☐ a little worthwhile ☐ not at all worthwhile

43. When thinking about the liver transplant, have you felt…

☐ very proud ☐ a little proud ☐ not at all proud

44. When you think about the transplant, have you felt…

☐ very brave ☐ a little brave ☐ not at all brave

45. When you think about the transplant, have you felt…

☐ very heroic ☐ a little heroic ☐ not at all heroic

46. Since the transplant, would you say you think…

☐ more highly of yourself—that you're a better person than before the transplant

☐ less highly of yourself, or

☐ there is no change in the way you think of yourself

7. How often do you think about having donated a part of your liver? Would you say you think about it…

☐ More than once a day ☐ Once a week
☐ Once a day ☐ Less often than once a week
☐ More than once a week ☐ Never

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8. I'm going to read you some statements about the donation experience. On a scale where 1 indicates that the statement is not at all true and 10 indicates that the statement is very true, tell me how you feel about each statement.

Since the donation…	Not at all true										Very true
a. I feel better about myself.	0	1	2	3	4	5	6	7	8	9	10
b. My family has expressed gratitude to me.	0	1	2	3	4	5	6	7	8	9	10
c. My family seems to hold me in higher esteem.	0	1	2	3	4	5	6	7	8	9	10
d. I feel I have helped my recipient in a significant way.	0	1	2	3	4	5	6	7	8	9	10
e. I feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10
f. My family relationships feel more difficult.	0	1	2	3	4	5	6	7	8	9	10
g. My life has special meaning.	0	1	2	3	4	5	6	7	8	9	10

Now I have some questions about your health since the donation.

9. Physically, how long did it take after the liver donation surgery before you felt completely back to normal? Would you say it took…

☐ 1 week
☐ 2 to 3 weeks
☐ 4 to 5 weeks
☐ 6 to 7 weeks
☐ 2 months
☐ 3 months
☐ 4 months
☐ 5 months
☐ 6 or more months
☐ you still do not feel back to normal

13. Compared to what you expected, would you say that your recovery was slower or faster than expected? Would you say it was…

☐ much slower than expected ☐ slower ☐ as expected ☐ faster ☐ much faster

11. Are there specific physical activities that you can't do as well as before the surgery?

☐ Yes ☐ No

↳ What are they?_____

12. How often do you worry about the physical effects on you of having donated a part of your liver?

☐ often ☐ sometimes ☐ almost never

19. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

20. Since the donation, have you developed any medical problems that you think are related to the donation surgery?

☐ Yes ☐ No

→ please describe _____

15. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

31. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

32. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

33. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if <u>your health now</u> limits you a lot, limits you a little, or does not limit you at all in these activities.
[IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing <u>several</u> flights of stairs	_____	_____	_____
e.	Climbing <u>one</u> flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking <u>more than a mile</u>	_____	_____	_____
h.	Walking <u>several hundred yards</u>	_____	_____	_____

i. Walking one hundred yards	_____	_____	_____
j. Bathing or dressing yourself	_____	_____	_____

34. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

35. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

21. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

22. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

23. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

27. The next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

25. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? Has it interfered…

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

26. Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

27. Here is a list of ways some people may feel physically after living organ donation. For each, please tell me if you have had the problem a lot, a little, or not at all in the past month.

	A LOT	A LITTLE	NOT AT ALL

	A LOT	A LITTLE	NOT AT ALL
a. Light headedness	1	2	3
b. Weakness	1	2	3
c. Tiredness	1	2	3
d. Bleeding at the site of the surgery	1	2	3
e. Pain at the site of the surgery	1	2	3
f. Itching at the site of the surgery	1	2	3
g. Tension around the site of the surgery	1	2	3
h. Numbness around the site of the surgery	1	2	3
i. Abdominal pain	1	2	3
j. Low back pain	1	2	3
k. Abdominal bloating or swelling	1	2	3
l. Decreased stomach tone	1	2	3
m. Puffiness in hands or feet	1	2	3
n. Leg swelling	1	2	3
o. Difficulty walking	1	2	3
p. Problems sleeping	1	2	3
q. Nausea or vomiting	1	2	3
r. Problems eating	1	2	3
s. Infection at the site of the surgery	1	2	3

28. I've asked you some general questions about pain. Now think about just the past 24 hours. In the **past 24 hours**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 29. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **past 24 hours**, pain has interfered with your:

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

29. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way in the past week.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

I'd like to turn now to how things have been with the transplant recipient and with other people.

33. First, what is your connection to the liver recipient? ***(RECORD WHETHER THE RECIPIENT IS THE DONOR'S SIBLING, PARENT, SPOUSE, FRIEND, ETC.)***:

Recipient is _____

31. How often do you think about your liver recipient, on average? Would you say it is…

☐ More than once a day ☐ Two or three times a month
☐ Once a day ☐ Once a month
☐ More than once a week ☐ Less than once a month

32. Is your liver recipient currently: ☐ alive ☐ no longer alive, or ☐ you don't know

IF RECIPIENT IS NO LONGER ALIVE:

a. How long after the donation did your recipient die?_____

b. Have you sought counseling since the death of your recipient? ☐ yes ☐ no

c. Thinking about your recipient's death, please tell me about how you feel about the outcome: On a 10 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "10" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you rate how you feel about the outcome

Not at all guilty 1 2 3 4 5 6 7 8 9 10 very guilty

IF RECIPIENT IS ALIVE:

d. How worried are you about your recipient?

□ very worried □ pretty worried □ not very worried □ not at all worried

e. How many times have you seen your recipient in the past year? _____ times

f. Would you like more contact or communication with your recipient?

□ yes, a lot more □ yes, a little more □ no

m. I'm going to read you some words that might describe your interactions with your liver recipient since the transplant. On a 7 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "7" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you describe your interactions with your liver recipient since the transplant?

Rewarding	1	2	3	4	5	6	7	Disappointing
Comfortable	1	2	3	4	5	6	7	Uncomfortable
Hard	1	2	3	4	5	6	7	Easy
Positive	1	2	3	4	5	6	7	Negative
Tense	1	2	3	4	5	6	7	Relaxed
Close	1	2	3	4	5	6	7	Distant
Awkward	1	2	3	4	5	6	7	Natural

h. Did your relationship with the recipient change after the transplant? Is your relationship with the recipient now…

□ much worse □ worse □ the same □ better □ much better

i. How would you rate the overall quality of your relationship with your recipient at this time? Would you say it is…

□ excellent □ very good □ average □ fair □ poor

j. Do you agree or disagree with this statement? "I feel closer to the recipient than I did before the transplant." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

q. Do you agree or disagree with this statement? "The recipient of my liver behaves in a way that risks the continued healthy functioning of the donated liver." Would you say you…

□ strongly agree □ agree □ neither agree nor disagree □ disagree □ strongly disagree

58. Compared to before the transplant, has your relationship with the rest of your family changed? Would you say it has…

□ Improved greatly

- ☐ Improved somewhat
- ☐ Stayed the same
- ☐ Gotten somewhat worse
- ☐ Gotten much worse

59. What about any relationship you have with a spouse or partner. First, what is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

60. ***[IF PARTICIPANT IS MARRIED/ LIVING WITH PARTNER AND SPOUSE/PARTNER IS NOT THE TRANSPLANT RECIPIENT AS PER ITEM #30 ABOVE]:*** If you were married to or living with this person at the time of your donation, has your relationship with him/her changed, compared to before the transplant? Has it…

- ☐ Improved greatly
- ☐ Improved somewhat
- ☐ Stayed the same
- ☐ Gotten somewhat worse
- ☐ Gotten much worse
- ☐ Not applicable: was not married/living with this person at the time of the transplant

61. The next questions focus on how the donation experience may have affected you. I'm going to read you a list of ways people sometimes feel after having donated a part of their liver for transplantation. Please tell me if you agree a lot, agree a little, disagree a little or disagree a lot with each statement.

a. Being a liver donor makes a person feel that he/she is somehow a bigger and more worthwhile person. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
b. A person willing to donate part of their liver is almost a hero. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
c. Donating a part of my liver was really sort of a high point in my life, making everything seem more meaningful. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

62. Please tell me if you experienced any of the following as a result of the donation, where a zero means you did not experience it, up to a 5, meaning that you experienced it to a very great degree.

	Did not experience this	Experienced this to a very great degree

	Did not experience this					Experienced this to a very great degree
a. I changed my priorities about what is important in life.	0	1	2	3	4	5
b. I have a greater appreciation for the value of my own life.	0	1	2	3	4	5
c. I am able to do better things with my life.	0	1	2	3	4	5
d. I have a better understanding of spiritual matters.	0	1	2	3	4	5
e. I have a greater sense of closeness with others.	0	1	2	3	4	5
f. I established a new path for my life.	0	1	2	3	4	5
g. I know better that I can handle difficulties.	0	1	2	3	4	5
h. I have a stronger religious faith.	0	1	2	3	4	5
i. I discovered that I'm stronger than I thought I was.	0	1	2	3	4	5
j. I learned a great deal about how wonderful people are.	0	1	2	3	4	5

Now I'd like to focus on how you've been feeling recently.

38. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

    complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

39. Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Little interest or pleasure in doing things.	1	2	3	4
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

40. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 41. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

41. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 42.

Have any of the following happened to you more than once in the last 6 months?

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

The next questions are about how you have dealt with financial issues related to your liver donation.

42. First, are you currently employed (in a paid position)?

- ☐ Working full time
- ☐ Working part time by choice
- ☐ Working part time due to disease or illness
- ☐ Not working due to disease or illness
- ☐ Not working because you can't find a job
- ☐ Retired

43. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

44. Since we last spoke with you, have you had to change jobs or modify your work because of your liver donation?

- ☐ No
- ☐ Yes, to a job with less manual labor
- ☐ Yes, to a less demanding or stressful job
- ☐ Yes, other changes: please describe:_____
- ☐ Not applicable because not employed before donation

45. Since we last spoke with you, have you had any changes in your income because of your liver donation?

☐ No, it has not changed ☐ Yes, it decreased ☐ Yes, it increased

46. Since we last spoke with you, have you had expenses related to your liver donation that were not covered by insurance? Tell me if you have had any of the following expenses due to the donation. ***(CHECK ALL THAT APPLY)***

- ☐ Lost wages
- ☐ Child or family members' care
- ☐ Transportation or parking costs
- ☐ Housing or lodging costs
- ☐ Food costs
- ☐ Medication costs not covered by any insurance
- ☐ Medical bills not covered by any insurance
- ☐ Other costs (list: _____)

47. Overall, how have the costs related to the donation compared to what you expected?

☐ less than expected ☐ more than expected ☐ about what was expected

48. Overall, have the costs related to the donation been a significant financial burden for you?

□ No, not a burden □ Yes, a mild burden □ Yes, a moderate burden □ Yes, a severe burden

49. Since we last spoke with you, have you had any of the following insurance problems because of the donation?

m. Did you have trouble keeping the health insurance that you already had?
- □ no
- □ yes, I had trouble but was able to keep my insurance
- □ yes, I lost my health insurance as a result of the donation
- □ not applicable (did not have insurance)

n. Did you have trouble getting new health insurance because of the donation?
- □ no
- □ yes, I had trouble but was able to get new insurance
- □ yes, I was denied new health insurance
- □ not applicable (did not try to get new health insurance)

c. Did you have trouble keeping the life insurance you already had because of the donation?
- □ no
- □ yes, I had trouble but was able to keep my life insurance
- □ yes, I lost my life insurance
- □ not applicable (did not have life insurance)

d. Did you have trouble getting new life insurance because of the donation?
- □ no
- □ yes, I had trouble but was able to get new life insurance
- □ yes, I was denied new life insurance
- □ not applicable (did not try to get new life insurance)

50. What type of medical insurance do you currently have? Please list all sources of coverage (for example, Medicare, Medicaid, private insurance, insurance through another family member, donation-related insurance).

_____

I have few questions about what you expect in the future. Here are some concerns that people sometimes have after donating an organ for transplantation. Please tell me tell me about whether you have any of these concerns.

51. How strongly do you agree or disagree with this statement: "Sometimes I worry that the liver donation will have negative effects on my health in the future." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

52. How strongly do you agree or disagree with this statement: "Since my liver donation, I worry that I will never feel physically 100% well again." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree
53. How strongly do you agree or disagree with this statement: "Knowing what I know now, I would donate again." Would you say you… ☐ strongly agree ☐ agree ☐ are unsure ☐ disagree ☐ strongly disagree

54. How would you rate your overall feelings about your liver donation? Would you say they are…

☐ Very positive ☐ Somewhat positive ☐ A little positive ☐ Neither positive nor negative ☐ A little negative ☐ Very negative

55. Do you somehow feel like a better person after having donated a part of your liver?

☐ yes ☐ no

56. Here is a list of ways some people feel about liver donors. Tell me which is the closest to the way you would describe a living liver donor.

☐ anyone who donated part of their liver could be called a hero

☐ a person who donates part of their liver makes an exceptional sacrifice

☐ anyone who donates part of their liver makes a sacrifice somewhat out of the ordinary

☐ it is generous to give part of your liver but anyone should do as much

Lastly, I have few standard background questions.

57. How many people usually live in your home, <u>including</u> yourself? ___ people

58. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, <u>tell me to stop when I get to the right one</u>.

☐ $10,000 or less
☐ $20,000 or less
☐ $30,000 or less
☐ $40,000 or less
☐ $50,000 or less
☐ $60,000 or less
☐ $70,000 or less
☐ $80,000 or less
☐ $90,000 or less
☐ $100,000 or less
☐ $110,000 or less
☐ $120,000 or less
☐ $130,000 or less
☐ $140,000 or less
☐ $150,000 or less
☐ more than $150,000

59. Is there anything else that you think would be important for us to know about how you've been doing since the donation?

_____

_____

_____

Thank you!

We'll put your $20 payment in the mail and we'll be calling you back next year for an update on how you're doing.

Prospective Cohort 2 Years Post-Donation*

Subject ID: _____ Date completed: _____

Hello, my name is _____ and I'm calling on behalf of the Adult to Adult Living Liver Transplantation Cohort Study. We called you a year ago and I'm calling again today to update some information since then. We want to learn about how you have been doing recently. Do you have about 35 to 45 minutes to complete the survey now? ***(IF YES, PROCEED. IF NO, SCHEDULE AN INTERVIEW TIME.)***

I want to remind you that everything you tell us is completely confidential and will not be associated with your name in any way. Neither the doctors, hospital staff, nor your families will see your answers—only the researchers and computer analysts. We will summarize all donors' answers in order to learn more about donors' well-being in the years after donation.

First, I have some questions about your opinions and feelings about the living donation process.

47. Looking back on the donation, in terms of the way you felt physically during and after the donation surgery, would you say that the donation was…

☐ very stressful ☐ pretty stressful ☐ not very stressful ☐ not at all stressful

48. Thinking about the liver transplant for which you donated, have you felt…

☐ very worthwhile ☐ a little worthwhile ☐ not at all worthwhile

49. When thinking about the liver transplant, have you felt…

☐ very proud ☐ a little proud ☐ not at all proud

50. When you think about the transplant, have you felt…

☐ very brave ☐ a little brave ☐ not at all brave

51. When you think about the transplant, have you felt…

☐ very heroic ☐ a little heroic ☐ not at all heroic

52. Since the transplant, would you say you think…

☐ more highly of yourself—that you're a better person than before the transplant

☐ less highly of yourself, or

☐ there is no change in the way you think of yourself

7. How often do you think about having donated a part of your liver? Would you say you think about it…

☐ More than once a day ☐ Once a week
☐ Once a day ☐ Less often than once a week
☐ More than once a week ☐ Never

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8. I'm going to read you some statements about the donation experience. On a scale where 1 indicates that the statement is not at all true and 10 indicates that the statement is very true, tell me how you feel about each statement.

Since the donation…	Not at all true										Very true
a. I feel better about myself.	0	1	2	3	4	5	6	7	8	9	10
b. My family has expressed gratitude to me.	0	1	2	3	4	5	6	7	8	9	10
c. My family seems to hold me in higher esteem.	0	1	2	3	4	5	6	7	8	9	10
d. I feel I have helped my recipient in a significant way.	0	1	2	3	4	5	6	7	8	9	10
e. I feel as if my life is more worthwhile.	0	1	2	3	4	5	6	7	8	9	10
f. My family relationships feel more difficult.	0	1	2	3	4	5	6	7	8	9	10
g. My life has special meaning.	0	1	2	3	4	5	6	7	8	9	10

Now I have some questions about your health since the donation.

9. Physically, how long did it take after the liver donation surgery before you felt completely back to normal? Would you say it took…

☐ 1 week
☐ 2 to 3 weeks
☐ 4 to 5 weeks
☐ 6 to 7 weeks
☐ 2 months
☐ 3 months
☐ 4 months
☐ 5 months
☐ 6 or more months
☐ you still do not feel back to normal

14. Compared to what you expected, would you say that your recovery was slower or faster than expected? Would you say it was…

☐ much slower than expected ☐ slower ☐ as expected ☐ faster ☐ much faster

11. Are there specific physical activities that you can't do as well as before the surgery?

☐ Yes ☐ No

↳ What are they?_____

12. How often do you worry about the physical effects on you of having donated a part of your liver?

☐ often ☐ sometimes ☐ almost never

21. Would you say you are…

☐ very worried about your own health now ☐ somewhat worried ☐ a little worried ☐ not at all worried

22. Since the donation, have you developed any medical problems that you think are related to the donation surgery?

☐ Yes ☐ No

→ please describe _____

15. What medications are you taking now? (***INCLUDING VITAMINS, OVER-THE-COUNTER AND HERBAL MEDICATIONS***):

_____

_____

36. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

37. Compared to one year ago, how would you rate your health in general now. Is it…

☐ Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago

38. Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if <u>your health now</u> limits you a lot, limits you a little, or does not limit you at all in these activities.
[IF RESPONDENT SAYS HE/SHE DOES NOT DO ACTIVITY, PROBE: IS THAT BECAUSE OF YOUR HEALTH?]

		YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a.	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	_____	_____	_____
b.	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	_____	_____	_____
c.	Lifting or carrying groceries	_____	_____	_____
d.	Climbing <u>several</u> flights of stairs	_____	_____	_____
e.	Climbing <u>one</u> flight of stairs	_____	_____	_____
f.	Bending, kneeling, or stooping	_____	_____	_____
g.	Walking <u>more than a mile</u>	_____	_____	_____
h.	Walking <u>several hundred yards</u>	_____	_____	_____

i. Walking one hundred yards	_____	_____	_____
j. Bathing or dressing yourself	_____	_____	_____

39. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work or other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

40. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems, such as feeling depressed or anxious? ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

21. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbors, or groups? Have they interfered...

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

22. How much bodily pain have you had during the past 4 weeks? Have you had…

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

23. During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere...

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

28. The next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… ***[READ EACH ITEM AND RESPONSE CHOICES]***

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of life?	____	____	____	____	____	____
b. Have you been very nervous?	____	____	____	____	____	____
c. Have you felt so down in the dumps that nothing could cheer you up?	____	____	____	____	____	____
d. Have you felt calm and peaceful?	____	____	____	____	____	____
e. Did you have a lot of energy?	____	____	____	____	____	____
f. Have you felt downhearted and depressed?	____	____	____	____	____	____
g. Did you feel worn out?	____	____	____	____	____	____
h. Have you been happy?	____	____	____	____	____	____
i. Did you feel tired?	____	____	____	____	____	____

25. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? Has it interfered…

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

26. Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a little easier than other people	____	____	____	____	____
b. I am as healthy as anybody I know	____	____	____	____	____
c. I expect my health to get worse	____	____	____	____	____
d. My health is excellent	____	____	____	____	____

27. Here is a list of ways some people may feel physically after living organ donation. For each, please tell me if you have had the problem a lot, a little, or not at all in the past month.

	A LOT	A LITTLE	NOT AT ALL

	A LOT	A LITTLE	NOT AT ALL
a. Light headedness	1	2	3
b. Weakness	1	2	3
c. Tiredness	1	2	3
d. Bleeding at the site of the surgery	1	2	3
e. Pain at the site of the surgery	1	2	3
f. Itching at the site of the surgery	1	2	3
g. Tension around the site of the surgery	1	2	3
h. Numbness around the site of the surgery	1	2	3
i. Abdominal pain	1	2	3
j. Low back pain	1	2	3
k. Abdominal bloating or swelling	1	2	3
l. Decreased stomach tone	1	2	3
m. Puffiness in hands or feet	1	2	3
n. Leg swelling	1	2	3
o. Difficulty walking	1	2	3
p. Problems sleeping	1	2	3
q. Nausea or vomiting	1	2	3
r. Problems eating	1	2	3
s. Infection at the site of the surgery	1	2	3

28. I've asked you some general questions about pain. Now think about just the past 24 hours. In the **past 24 hours**, how much abdominal or back pain have you had? Please tell me on a scale of 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

IF RESPONDENT ENDORSED "0" (NO PAIN), SKIP TO Q. 29. OTHERWISE ASK THE FOLLOWING QUESTIONS:

On a scale of 0 to 10, what number best describes how, during the **past 24 hours**, pain has interfered with your:

	Does not interfere										Completely interferes
a. General activity	0	1	2	3	4	5	6	7	8	9	10
b. Mood	0	1	2	3	4	5	6	7	8	9	10
c. Walking ability	0	1	2	3	4	5	6	7	8	9	10
d. Normal work (including both work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
e. Relations with other people	0	1	2	3	4	5	6	7	8	9	10
f. Sleep	0	1	2	3	4	5	6	7	8	9	10
g. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

29. Earlier I asked you some general questions about fatigue or tiredness that you may have experienced. Now think about just the past week. For each statement that I'll read to you, please tell me how much you have felt this way in the past week.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A LOT	VERY MUCH
a. I feel fatigued.	1	2	3	4	5
b. I feel weak all over.	1	2	3	4	5
c. I feel listless or "washed out."	1	2	3	4	5
d. I feel tired.	1	2	3	4	5
e. I have trouble starting things because I am tired.	1	2	3	4	5
f. I have trouble finishing things because I am tired.	1	2	3	4	5
g. I have energy.	1	2	3	4	5
h. I am able to do my usual activities.	1	2	3	4	5
i. I need to sleep during the day.	1	2	3	4	5
j. I am too tired to eat.	1	2	3	4	5
k. I need help doing my usual activities.	1	2	3	4	5
l. I am frustrated by being too tired to do the things I want to do.	1	2	3	4	5
m. I have to limit my social activity because I am tired.	1	2	3	4	5

I'd like to turn now to how things have been with the transplant recipient and with other people.

34. First, what is your connection to the liver recipient? ***(RECORD WHETHER THE RECIPIENT IS THE DONOR'S SIBLING, PARENT, SPOUSE, FRIEND, ETC.)***:

Recipient is _____

31. How often do you think about your liver recipient, on average? Would you say it is…

☐ More than once a day ☐ Two or three times a month
☐ Once a day ☐ Once a month
☐ More than once a week ☐ Less than once a month

32. Is your liver recipient currently: ☐ alive ☐ no longer alive, or ☐ you don't know

IF RECIPIENT IS NO LONGER ALIVE:

a. How long after the donation did your recipient die?_____

b. Have you sought counseling since the death of your recipient? ☐ yes ☐ no

c. Thinking about your recipient's death, please tell me about how you feel about the outcome: On a 10 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "10" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you rate how you feel about the outcome

Not at all guilty 1 2 3 4 5 6 7 8 9 10 very guilty

IF RECIPIENT IS ALIVE:

d. How worried are you about your recipient?

□ very worried □ pretty worried □ not very worried □ not at all worried

e. How many times have you seen your recipient in the past year? _____ times

f. Would you like more contact or communication with your recipient?

□ yes, a lot more □ yes, a little more □ no

n. I'm going to read you some words that might describe your interactions with your liver recipient since the transplant. On a 7 point scale where "1" is _____ ***(INSERT FIRST ADJECTIVE)*** and "7" is _____ ***(INSERT SECOND ADJECTIVE)***, how would you describe your interactions with your liver recipient since the transplant?

Rewarding	1	2	3	4	5	6	7	Disappointing
Comfortable	1	2	3	4	5	6	7	Uncomfortable
Hard	1	2	3	4	5	6	7	Easy
Positive	1	2	3	4	5	6	7	Negative
Tense	1	2	3	4	5	6	7	Relaxed
Close	1	2	3	4	5	6	7	Distant
Awkward	1	2	3	4	5	6	7	Natural

h. Did your relationship with the recipient change after the transplant? Is your relationship with the recipient now…

□ much worse □ worse □ the same □ better □ much better

i. How would you rate the overall quality of your relationship with your recipient at this time? Would you say it is…

□ excellent □ very good □ average □ fair □ poor

j. Do you agree or disagree with this statement? "I feel closer to the recipient than I did before the transplant." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

r. Do you agree or disagree with this statement? "The recipient of my liver behaves in a way that risks the continued healthy functioning of the donated liver." Would you say you…

□ strongly agree □ agree □ neither agree nor disagree □ disagree □ strongly disagree

63. Compared to before the transplant, has your relationship with the rest of your family changed? Would you say it has…

□ Improved greatly

- ☐ Improved somewhat
- ☐ Stayed the same
- ☐ Gotten somewhat worse
- ☐ Gotten much worse

64. What about any relationship you have with a spouse or partner. First, what is your current marital status? ***(CHOOSE ONE)***

☐ single (never married) ☐ married ☐ living with long-term partner ☐ divorced ☐ separated ☐ widowed

65. ***[IF PARTICIPANT IS MARRIED/ LIVING WITH PARTNER AND SPOUSE/PARTNER IS NOT THE TRANSPLANT RECIPIENT AS PER ITEM #30 ABOVE]:*** If you were married to or living with this person at the time of your donation, has your relationship with him/her changed, compared to before the transplant? Has it…

- ☐ Improved greatly
- ☐ Improved somewhat
- ☐ Stayed the same
- ☐ Gotten somewhat worse
- ☐ Gotten much worse
- ☐ Not applicable: was not married/living with this person at the time of the transplant

66. The next questions focus on how the donation experience may have affected you. I'm going to read you a list of ways people sometimes feel after having donated a part of their liver for transplantation. Please tell me if you agree a lot, agree a little, disagree a little or disagree a lot with each statement.

a. Being a liver donor makes a person feel that he/she is somehow a bigger and more worthwhile person. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
b. A person willing to donate part of their liver is almost a hero. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot
c. Donating a part of my liver was really sort of a high point in my life, making everything seem more meaningful. Do you… ☐ agree a lot ☐ agree a little ☐ disagree a little ☐ disagree a lot

67. Please tell me if you experienced any of the following as a result of the donation, where a zero means you did not experience it, up to a 5, meaning that you experienced it to a very great degree.

	Did not experience this	Experienced this to a very great degree

	Did not experience this					Experienced this to a very great degree
a. I changed my priorities about what is important in life.	0	1	2	3	4	5
b. I have a greater appreciation for the value of my own life.	0	1	2	3	4	5
c. I am able to do better things with my life.	0	1	2	3	4	5
d. I have a better understanding of spiritual matters.	0	1	2	3	4	5
e. I have a greater sense of closeness with others.	0	1	2	3	4	5
f. I established a new path for my life.	0	1	2	3	4	5
g. I know better that I can handle difficulties.	0	1	2	3	4	5
h. I have a stronger religious faith.	0	1	2	3	4	5
i. I discovered that I'm stronger than I thought I was.	0	1	2	3	4	5
j. I learned a great deal about how wonderful people are.	0	1	2	3	4	5

Now I'd like to focus on how you've been feeling recently.

38. On a scale where 1 indicates complete dissatisfaction and 7 indicates complete satisfaction, which number comes closest to how you feel about your life as a whole these days?

    complete dissatisfaction 1 2 3 4 5 6 7 complete satisfaction.

40. Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Little interest or pleasure in doing things.	1	2	3	4
b. Feeling down, depressed, or hopeless.	1	2	3	4
c. Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
d. Feeling tired or having little energy.	1	2	3	4
e. Poor appetite or overeating.	1	2	3	4
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	1	2	3	4
g. Trouble concentrating on things, such as reading the newspaper or watching television.	1	2	3	4

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
h. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4
i. Thoughts that you would be better off dead or of hurting yourself in some way.	1	2	3	4

40. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
a. Feeling nervous, anxious, or on edge, or worrying a lot about different things.	1	2	3	4
IF RESPONDENT ANSWERS "NOT AT ALL" GO TO Q. 41. OTHERWISE CONTINUE:				
b. Feeling restless so that it is hard to sit still.	1	2	3	4
c. Getting tired very easily.	1	2	3	4
d. Muscle tension, aches, or soreness.	1	2	3	4
e. Trouble falling asleep or staying asleep.	1	2	3	4
f. Trouble concentrating on things, like reading a book or watching TV.	1	2	3	4
g. Becoming easily annoyed or irritable.	1	2	3	4

41. Do you ever drink alcohol (including beer or wine)?..... NO [ ] YES [ ]

IF RESPONDENT ANSWERS "NO", GO TO Q. 42.

Have any of the following happened to you more than once in the last 6 months?

	YES	NO
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health?	1	2
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities?	1	2
c. You missed or were late for work, school, or other activities because you were drinking or hung over?	1	2
d. You had a problem getting along with other people while you were drinking?	1	2
e. You drove a car after having several drinks or after drinking too much?	1	2

The next questions are about how you have dealt with financial issues related to your liver donation.

42. First, are you currently employed (in a paid position)?

- ☐ Working full time
- ☐ Working part time by choice
- ☐ Working part time due to disease or illness
- ☐ Not working due to disease or illness
- ☐ Not working because you can't find a job
- ☐ Retired

43. What is your current occupation? (Or, if you're not employed now, what occupation did you have when you last worked outside of the home?)

_____

44. Since we last spoke with you, have you had to change jobs or modify your work because of your liver donation?

- ☐ No
- ☐ Yes, to a job with less manual labor
- ☐ Yes, to a less demanding or stressful job
- ☐ Yes, other changes: please describe:_____
- ☐ Not applicable because not employed before donation

47. Since we last spoke with you, have you had any changes in your income because of your liver donation?

☐ No, it has not changed ☐ Yes, it decreased ☐ Yes, it increased

48. Since we last spoke with you, have you had expenses related to your liver donation that were not covered by insurance? Tell me if you have had any of the following expenses due to the donation. ***(CHECK ALL THAT APPLY)***

- ☐ Lost wages
- ☐ Child or family members' care
- ☐ Transportation or parking costs
- ☐ Housing or lodging costs
- ☐ Food costs
- ☐ Medication costs not covered by any insurance
- ☐ Medical bills not covered by any insurance
- ☐ Other costs (list: _____)

47. Overall, how have the costs related to the donation compared to what you expected?

☐ less than expected ☐ more than expected ☐ about what was expected

48. Overall, have the costs related to the donation been a significant financial burden for you?

□ No, not a burden □ Yes, a mild burden □ Yes, a moderate burden □ Yes, a severe burden

50. Since we last spoke with you, have you had any of the following insurance problems because of the donation?

o. Did you have trouble keeping the health insurance that you already had?
- □ no
- □ yes, I had trouble but was able to keep my insurance
- □ yes, I lost my health insurance as a result of the donation
- □ not applicable (did not have insurance)

p. Did you have trouble getting new health insurance because of the donation?
- □ no
- □ yes, I had trouble but was able to get new insurance
- □ yes, I was denied new health insurance
- □ not applicable (did not try to get new health insurance)

c. Did you have trouble keeping the life insurance you already had because of the donation?
- □ no
- □ yes, I had trouble but was able to keep my life insurance
- □ yes, I lost my life insurance
- □ not applicable (did not have life insurance)

d. Did you have trouble getting new life insurance because of the donation?
- □ no
- □ yes, I had trouble but was able to get new life insurance
- □ yes, I was denied new life insurance
- □ not applicable (did not try to get new life insurance)

50. What type of medical insurance do you currently have? Please list all sources of coverage (for example, Medicare, Medicaid, private insurance, insurance through another family member, donation-related insurance).

_____

I have few questions about what you expect in the future. Here are some concerns that people sometimes have after donating an organ for transplantation. Please tell me tell me about whether you have any of these concerns.

51. How strongly do you agree or disagree with this statement: "Sometimes I worry that the liver donation will have negative effects on my health in the future." Would you say you…

□ strongly agree □ agree □ disagree □ strongly disagree

52. How strongly do you agree or disagree with this statement: "Since my liver donation, I worry that I will never feel physically 100% well again." Would you say you…

☐ strongly agree ☐ agree ☐ disagree ☐ strongly disagree
53. How strongly do you agree or disagree with this statement: "Knowing what I know now, I would donate again." Would you say you… ☐ strongly agree ☐ agree ☐ are unsure ☐ disagree ☐ strongly disagree

57. How would you rate your overall feelings about your liver donation? Would you say they are…

☐ Very positive ☐ Somewhat positive ☐ A little positive ☐ Neither positive nor negative ☐ A little negative ☐ Very negative

58. Do you somehow feel like a better person after having donated a part of your liver?

☐ yes ☐ no

59. Here is a list of ways some people feel about liver donors. Tell me which is the closest to the way you would describe a living liver donor.

☐ anyone who donated part of their liver could be called a hero

☐ a person who donates part of their liver makes an exceptional sacrifice

☐ anyone who donates part of their liver makes a sacrifice somewhat out of the ordinary

☐ it is generous to give part of your liver but anyone should do as much

Lastly, I have few standard background questions.

57. How many people usually live in your home, <u>including</u> yourself? ___ people

58. Please consider the following categories and tell me which one best describes your total household income for the past year, including salaries, wages, medical disability, and any other income. As I read the categories, <u>tell me to stop when I get to the right one</u>.

☐ $10,000 or less
☐ $20,000 or less
☐ $30,000 or less
☐ $40,000 or less
☐ $50,000 or less
☐ $60,000 or less
☐ $70,000 or less
☐ $80,000 or less
☐ $90,000 or less
☐ $100,000 or less
☐ $110,000 or less
☐ $120,000 or less
☐ $130,000 or less
☐ $140,000 or less
☐ $150,000 or less
☐ more than $150,000

59. Is there anything else that you think would be important for us to know about how you've been doing since the donation?

_____

_____

_____

Thank you!

This is our final interview with you. We'll put your $20 payment in the mail.

Donor Pain Study - Patient Information and Assent

Dear Sir \ Madam,

We would be grateful if you would participate in our survey on how patients feel after surgery. The aim of the survey is to improve management of pain after live donor surgery.

The information you provide will be made anonymous once you hand in this questionnaire. This means that your name or other form of identification will be deleted from the questionnaire after you hand it in and will not be included in any records we will have.

Your answers in this questionnaire will not be shared with your medical or nursing team.

We can assure you that your team will treat you in the same way whether or not you choose to participate in our survey.

Many thanks for considering to take part in this survey.

Name of Person Administering Survey

Subject ID D

A2ALL Donor Pain Survey

PRINT FORM

Date of First Attempt Time AM PM

Sedation Score

- 0 = Fully Awake
- 1 = Light sedation, largely aware of self/surroundings. Mildly sleepy
- 2 = Moderate sedation, slightly aware of self/surrounds. Somnolent but easily aroused.
- 3 = Deeply sedated, unaware of self/surroundings.
- 4 = General anesthesia, patient is unconscious.

Type of Pain Management (check all that apply)

- Epidural
- Intrathecal
- IVPCA
- Local Infiltration
- Other

Date of Second Attempt Time AM PM Sedation Score

P1. On this scale, please indicate the **least** pain you had in the **FIRST 24 hours**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P1A. On this scale, please indicate the **least** pain you had in the **LAST 24 hours**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P2. On this scale, please indicate the **worst** pain you had in the **LAST 24 hours.**

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P3. What percentage of time in the **LAST 24 hours** were you in **severe pain**?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Never in severe pain										Always in severe pain

Subject ID D

P4. Choose the **one** number below that best describes how much pain **interfered or prevented you from:**

a. Doing **activities in bed** such as turning, sitting up, repositioning:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

b. Doing **activities out of bed** such as walking, sitting in a chair, standing at the sink:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

c. ***Falling*** **asleep:**

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

d. ***Staying*** **asleep:**

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

P5. Pain can affect our mood and emotions.
On this scale, please choose the **one** number that best shows how much the pain has caused you to feel:

a. Anxious

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

b. Depressed

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

c. Frightened

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

Subject ID D

P5. (Cont'd)
On this scale, please choose the **one** number that best shows how much pain caused you to feel:

d. Helpless

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

P6. Have you had any of the following side effects?
Please choose "0" if no; if yes, choose the **one** number that best shows the severity of each:

a. Nausea

0	1	2	3	4	5	6	7	8	9	10
None										Severe

b. Drowsiness

0	1	2	3	4	5	6	7	8	9	10
None										Severe

c. Itching

0	1	2	3	4	5	6	7	8	9	10
None										Severe

d. Dizziness

0	1	2	3	4	5	6	7	8	9	10
None										Severe

P7. In the last 24 hours, how complete has your pain **relief** been?
Please choose the **one** percentage that best shows how much relief you have received from all of your pain treatments combined (medicine and non-medicine treatments).

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

Subject ID D

P8. Were you **allowed to participate in decisions** about your pain treatment as much as you wanted to?

0	1	2	3	4	5	6	7	8	9	10
Not at all										Very much so

P9. Choose the **one** number that best shows how **satisfied** you are with the results of your pain treatment while in the hospital.

0	1	2	3	4	5	6	7	8	9	10
Extremely Dissatisfied										Extremely Satisfied

P10. Did you receive any **information** about your pain treatment options? ◯ Yes ◯ No

a. If yes, please choose the number that best shows **how helpful** the information was.

0	1	2	3	4	5	6	7	8	9	10
Not at all helpful										Extremely helpful

P11. Did you use any **non-medicine methods** to relieve your pain? ◯ Yes ◯ No

If yes, **check all** that apply:

- ☐ cold pack
- ☐ deep breathing
- ☐ distraction (such as watching TV, reading)
- ☐ heat
- ☐ imagery or visualization
- ☐ massage
- ☐ meditation
- ☐ listen to music
- ☐ prayer
- ☐ relaxation
- ☐ walking
- ☐ other (specify)

P12. How often did a nurse or doctor **encourage you to use** non-medication methods?

- ◯ never
- ◯ sometimes
- ◯ often

Thank you for your time and feedback!

Robert M. Merion, MD
Chair, A2ALL Steering Committee

August 13, 2013

Dear A2ALL Principal Investigator:

Amendment 2 of the A2ALL Core Protocol added Specific Aim 6, which is focused on studying donors' perception of their level of pain and the effectiveness of pain control strategies. The study is conducted via a questionnaire administered on the second post-donation day.

The protocol included an error in the exclusion criteria, specifying that subjects must be consented no less than 48 hours prior to the donation surgery. There is no clinical or research-related reason to exclude subjects who consent within 48 hours prior to donation surgery. Therefore, this exclusion criterion will be removed during the next IRB renewal.

This letter serves as an ongoing pre-approval for the inclusion of eligible donor subjects who give consent to participate in the Core Protocol less than 48 hours before their donation operation.

The protocol will be modified to include this clarification at a later date. Please contact the A2ALL Data Coordinating Center with any questions about this minor change.

Yours sincerely,

Robert Merion, MD, FACS
Chair, A2ALL Steering Committee

RMM/ja
CC: Study coordinator

340 East Huron St., Suite 300
Ann Arbor, MI 48104
Phone: (734) 369-9674, Fax: (734) 665-2103

DONOR BIOSAMPLE COLLECTION – CORE PROTOCOL

Sample Type	Time Point						
	Pre-Donation	At Donation		Post Donation			
	Shortly Pre-Donation	Just Prior to Resection*	1° Post Resection**	Day 7	Month 1	Month 3	Year 1
Liver Bx - Biorepository		**3 CORE BX IN RNA LATER - FROZEN**	**3 CORE BX IN RNA LATER - FROZEN**				
Whole Blood - Genetics Repository	**2 EDTA Tubes - AMBIENT†**						
Serum - Biorepository	**TEN 0.5ML ALIQUOTS - FROZEN**			**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**
Plasma - Biorespository	**FOUR 0.5ML ALIQUOTS - FROZEN**				**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**
Nonviable cells (for future cell proteomics) - Biorepository	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**				**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**
Viable cells resuspended in 10% DMSO & 90% FCS for Flow Cytometry or other studies (such as stimulation) at a future date - Biorespository	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**				**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**
Whole Blood - DNA Extraction for future study	**2 PAXGENE TUBES - FROZEN**				**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**

***The first biopsy is taken prior to re-section closeset to the line of re-section.**
****The second biopsy is taken 1° post reperfusion or just prior to closing.**
† 2 EDTA tubes for the DNA Core Lab can be collected at any ONE time (with Core Protocol Version 1.9 approval)
Note: Shortly pre-donation samples can be collected after subject receives anesthesia.

Sample Type	Time Point										
	Pre-Transplant	At Transplant		Post Transplant							
	Shortly Pre-Transplant	Back Table*	1° Post Reperfusion**	Day 7	Week 2	Month 1	Month 3	Year 1	Year 2	Year 3	Year 4***
Liver Bx - Biorepository		**3 CORE BX IN RNA LATER - FROZEN**	**3 CORE BX IN RNA LATER - FROZEN**								
Whole Blood - Genetics Repository	**2 EDTA TUBES - AMBIENT**										
Serum - Biorepository	**TEN 0.5ML ALIQUOTS - FROZEN**			**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**	**TEN 0.5ML ALIQUOTS - FROZEN**
Plasma - Biorespository	**FOUR 0.5ML ALIQUOTS - FROZEN**					**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**	**FOUR 0.5ML ALIQUOTS - FROZEN**		
Nonviable cells (for future cell proteomics) - Biorepository	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**					**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN RNALater - FROZEN**		
Viable cells resuspended in 10% DMSO & 90% FCS for Flow Cytometry or other studies (such as stimulation) at a future date - Biorespository	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**					**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**	**THREE 0.5ML ALIQUOTS CELLS SUSPENDED IN 10% DMSO & 90% FCS - FROZEN**		
Whole Blood - RNA Extraction for future study	**2 PAXGENE TUBES - FROZEN**					**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**	**2 PAXGENE TUBES - FROZEN**		

* Biopsy is taken from the donated graft while on the back table prior to implanting into recipient.

**Biopsy is taken from the donated graft after reperfusion is complete.

*** All subsequent annual visits collect the same biosamples.

A2ALL Core Protocol Recipient Biosample Collection 8/3/2011

Assembling the A2ALL E65 Repository Shipper

1. Place up to 81 x 2 ml vials in each 2-inch high specimen box. Place the vials in the specimen box from left to right, top to bottom. Group vials by patient and visit.	
2. Place each specimen box and an absorbent sheet inside a plastic biohazard bag (part # STP 711). Seal the bag.	
3. Place each plastic bag inside a white tuck-and-fold envelope (part # STP 714). Place the box inside the long pocket of the envelope.	
4. Crease the envelope near the middle, fold the envelope over and tuck the end of the envelope containing the box inside the short pocket on the opposite side of the envelope.	
5. Push the box firmly into the short pocket of the envelope.	
6. Place up to 49 PAXgene™ tubes in the 3-inch high specimen box. Place the tubes in the specimen box from left to right, top to bottom.	

Assembling the A2ALL E65 Repository Shipper

7. Place the PAXgene™ tube specimen box and absorbent sheet inside the large plastic biohazard bag (part # STP 731). Seal the bag. Place the large plastic biohazard bag inside the large envelope (part # 730). Seal the envelope.

8. Place a thin layer of dry ice in the bottom of the shipping box. Place up to 5 specimen boxes with cryovials and 1 specimen box with PAXgene™ tubes on the dry ice.

9. Fill the remaining space in the shipper with dry ice, leaving about 3 inches of space at the top for the foam insert.

10. Place the foam insert on top of the dry ice in the opening. Set a copy of the shipment log on top of the foam insert. Close and tape the outer box.

11. Attach all shipping labels to the same side of the box.
    - On the Class 9 dry ice label, enter the following: “1” next to “number pkgs” and the weight of the package in kilograms; weight of dry ice in kilograms; shipper’s name and address; consignee’s name and address
    - Affix the Class 9 label to the side of the box in the upper right corner.
    - Affix your organization’s “From” address label just to the right of the “Up” arrows.
    - Affix the repository “To” address label just below the “From” address label.
    - Affix the UN 3373 label below the dry ice label. Orient the label as a diamond.
    - Affix a label with “Person responsible” and the name and phone number of the person responsible for the shipment. Place the label below the repository “To” address label.
    - Labels should not overlap each other or wrap around a corner of the box.

Assembling the A2ALL E65 Repository Shipper

12. Complete the pre-printed FedEx air bill to ship specimens to the NIDDK Biosample Repository.
    - Section 1, From: Enter the date of shipment, your name, phone number and return address. Leave "Sender's FedEx Account Number" blank.
    - Section 6, Special Handling: Check "Yes, Shipper's Declaration not required." Check the block next to "Dry Ice" and enter "1" and the weight of dry ice in kilograms.
    - Section 7, Payment: Enter "1" under "Total Packages" and the total weight of the package in pounds.
    - Follow the peel-and-stick instructions on the back of the air bill. Affix the air bill to the left of the UN3373 label
13. If your organization does not have a daily scheduled FedEx pickup, call FedEx at 1-800-GO-FEDEX (1-800-463-3339). Give them the account number on the preprinted FedEx air bill (in Section 7, Payment) and your pickup address. FedEx will dispatch a courier to pick up the package. **Please schedule shipments Monday through Wednesday to avoid weekend shipment delays. Ship all samples via FedEx Priority Overnight service. Do not ship samples on Friday. The NIDDK Biosample Repository is closed on weekends.**
14. Send a shipment notification to the repository at **bio-niddkrepository@thermofisher.com** on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number and attach an electronic copy of the shipment log as an Excel or CSV file.
15. Contact us by email at the above email address or call Heather Higgins (240-686-4703) or Sandra Ke (240-686-4702) for questions regarding packaging and shipping.

ThermoFisher SCIENTIFIC

A2ALL Supply Order System

Fisher BioServices

The world leader in serving science

Initial Supply Order

- Once a site is activated, Fisher BioServices will send collection kits to your site.
- It will be the responsibility of each site to order additional collection/serum shipper kits.
- It is important to order the kits as early as possible before they are needed.
- It will take approximately 7 business days for delivery.
- Do not wait until you are out of kits before placing the order for replenishment.

Supply Order System

- Once your site is activated, you will receive an email with the system web site address and log-in information. You will be directed to the main log-in page below. Enter User ID and Password.

Initial Log-in and Home Page

- You will be directed to change your password (optional; can remain the default, if preferred).
- After log-in, the Home Page will appear. To place an order, click “Add New Supply Order”.

Placing an Order

- Select a date for delivery (site arrival date); click calendar or manual entry. Schedule shipment, at minimum, 7 business days from today’s date.
- Click “Proceed”.

Placing an Order Continued

- Verification of date for delivery. Allows you to change date.

Placing an Order Continued

- If applicable, select appropriate Protocol (example of kit types will appear).

Placing an Order Continued

- Read statement in box below purple Warning box, and then click purple box (ignore "Site Arrival Time" and "Purchase Order Number" options).

Placing an Order Continued

- Click "OK" on pop-up box after reading statement.

Placing an Order Continued

- Add any special instructions/notes for the Shipping Department (do not include specifications about the shipping site) and click "Save Special Instructions" or, if no instructions necessary, click "Skip Instructions".

Placing an Order Continued

- Order Screen will appear. Select "Ship-To Site" from drop-down menu.
- Page will automatically reload, with shipping address listed.

Placing an Order Continued

- Enter quantity of kits requested.

Placing an Order Continued

- Click off "Units Ordered" box (anywhere else on page) and page will automatically reload to capture requested quantity.

Placing an Order Continued

- Click "Finished Entering Items" (blue box) to continue.

Placing an Order Continued

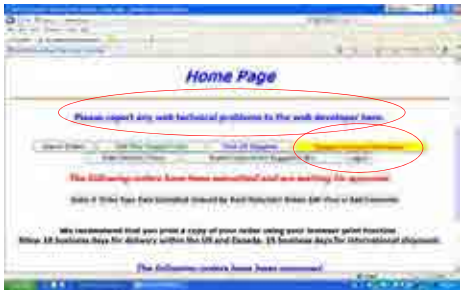
- Order Summary Screen will appear.
- Must click "Submit Order" (blue box) to complete order.

Order Status

- After an order has been placed the status can be viewed from the Home Page (will also receive e-mail confirmation).
- "Order Status" indicates where FBS is at in the process (Acknowledged, Shipped, etc.)

Need Assistance? Technical Issues?

- Technical issues – click on contact IT.
- For contact information (Project Manager, IT), click yellow box.



Summary

- Initial supply order will be sent to site after activation.
- Place orders for collection and/or serum shipper kits using the on-line Supply Order System (SOS). **Be sure to click "Submit Order" button on Order Form Summary page.**
- Place orders in advance of actual need.
- Order status can be tracked using the SOS. Once order is shipped, you will receive an e-mail with tracking information (can also click on Order Number on Home Page to track shipment).
- Additional training to be provided to each site if required.

HANDLING AND ONSITE STORAGE OF EDTA TUBES POST COLLECTION FOR A2ALL-2

1. Immediately after collecting blood, invert the EDTA tubes 8-10 times. Do not shake. Vigorous mixing may cause foaming or hemolysis.
2. Store filled EDTA tubes at 2^{o} – 8^{o}C until ready to ship.

PACKAGING INSTRUCTIONS FOR A2ALL-2 REFRIGERATED BLOOD SHIPMENT

NOTE: The return shipper can be used to ship up to 8 EDTA tubes (4 patients) at one time.

1. Place the 2 gel packs in refrigerator (2^{o} – 8^{o}C) overnight before using. DO NOT FREEZE.
2. Remove white absorbent pouch from 95 kPa plastic bag.
3. Place one EDTA vacutainer tube into each slot of absorbent pouch (see picture below). A second 4-tube pouch is provided for shipping up to 8 tubes at one time.

4. Place up to 2 absorbent pouches containing the EDTA tubes into the 95 kPa bag and seal by following the instructions on the outside of the bag. Remove as much air as possible prior to sealing kPa bag (see picture below).

5. Place 95 kPa bag into bottom of Styrofoam shipper (see picture below).

6. Remove **2** pre-conditioned **refrigerated** gel packs from the refrigerator and place on top of 95 kPa bag containing the samples (see picture below).

7. Replace Styrofoam lid.
8. Place any paperwork on top of Styrofoam lid. Close cardboard box and seal.
9. Place UN3373 label on the front of box (see picture below).

10. Fill out Site address information and shipment date in section 1 on pre-filled/pre-paid FedEx airbill. Keep top copy of airbill and place remaining copies into airbill holder. **(International sites, please use pre-filled FedEx International airbill. Additional paperwork and/or requirements for Customs are the responsibility of the sender.)**
11. Attach airbill holder to top of shipping box.
12. Ship package via Federal Express Priority Overnight or International Priority.
13. Before faxing the "Shipment Receipt Confirmation" to the DCC, please email the DCC monitors at a2all-monitors@umich.edu regarding the forthcoming confirmation sheet. Alternatively, if possible please scan and email the confirmation sheet to the DCC monitors instead (please use same a2all-monitors email address noted here).

RNA*later*®

Tissue Collection: RNA Stabilization Solution

Catalog #7020 (100 ml), #7024 (250 ml), #7021 (500 ml), #7022 (50 x 1.5 ml), #7023 (20 x 5 ml)

Protocol

Ambion® THE RNA COMPANY™

A. Product Description

RNA*later*® is an aqueous, non-toxic tissue storage reagent that rapidly permeates tissue to stabilize and protect cellular RNA in situ in ***unfrozen*** specimens. Tissue pieces are harvested and immediately submerged in RNA*later* for storage without jeopardizing the quality or quantity of RNA. RNA*later* eliminates the need to immediately process tissue specimens or to freeze samples in liquid nitrogen for later processing. The figures below show 2 common experiments using RNA isolated from RNA*later*-preserved samples.

RNA*later* preserves RNA in tissues for up to 1 day at 37˚C, 1 week at 25˚C, and 1 month or more at 4˚C. Tissues can also be stored at –20˚C or at –80˚C long-term.

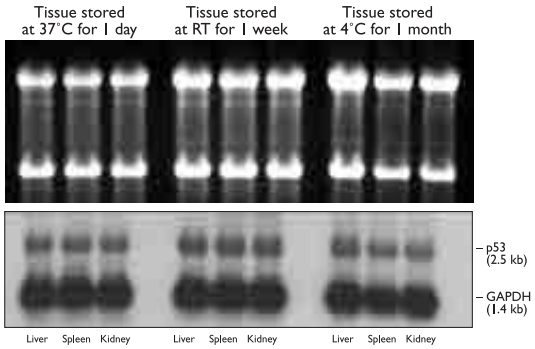


Figure 1. RNA from Tissue Stored in RNA*later*

RNA was extracted from mouse tissues stored in RNA*later* as shown. The top panel is an ethidium bromide-stained denaturing agarose gel; the bottom panel shows a Northern blot.

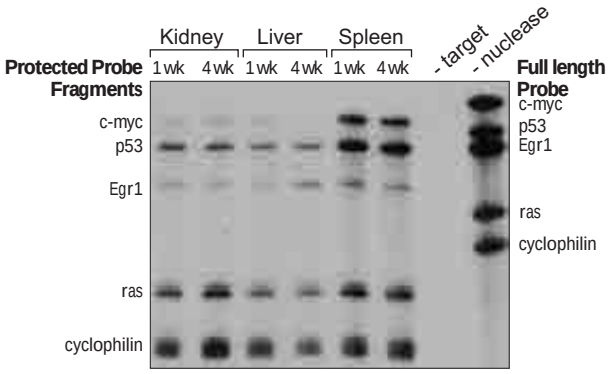


Figure 2. mRNA profiles of mouse tissues stored in RNA*later*

The indicated mouse tissues were stored in RNA*later* for 1 or 4 weeks at 4˚C. RNA was isolated from each tissue and analysed using Ambion's RPA III™ kit. 10 µg of RNA was hybridized with a mixture of $5x10^4$ cpm of each of 5 antisense probes. The gel was exposed to film for 4 hours at –80˚C with an intensifying screen.

Storage and Stability

Store RNA*later* at room temperature. It is guaranteed for 6 months from the date received.

If any precipitation of RNA*later* is seen, heat the solution to 37˚C and agitate to redissolve it.

What materials have been tested in RNA*later*?

RNA*later* has been extensively tested on tissues from several vertebrate species. These include brain, heart, kidney, spleen, liver, testis, skeletal muscle, fat, lung and thymus. RNA*later* is also effective for *E. Coli*, *Drosophila*, tissue culture cells, white blood cells, and some plants.

Will RNA*later* work with my RNA Isolation Kit?

RNA*later* is compatible with most RNA isolation methods. Specifically, we have used RNA*later*-preserved samples with TRI Reagent®1, and all of Ambion's RNA isolation kits and reagents, including: RNAwiz™ (one-step disruption/separation reagent), TōTALLY RNA™ (guanidinium isothiocynate disruption, acid phenol extraction), RNAqueous™ (phenol-free, glass fiber filter binding), PARIS™ (Protein and RNA Isolation System), *mir*Vana™ miRNA Isolation Kit (glass fiber filter microRNA isolation), and MicroPoly(A)Pure™ (direct isolation of poly(A) RNA from guanidinium lysate).

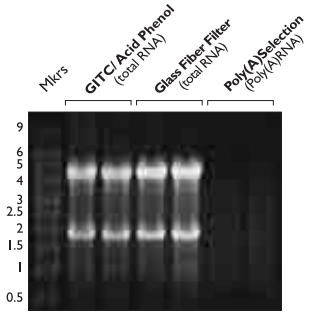


Figure 3. RNA isolated from tissue stored in RNA*later* using different isolation methods

Whole mouse hearts and livers were dissected, and placed in RNA*later*, in which they were stored for 3 days at 4˚C. RNA was isolated from equal mass amounts of each tissue using the indicated Ambion kits. RNA (5 µg) was run on denaturing agarose, stained with ethidium bromide.

Can genomic DNA be obtained from RNA*later*-stored samples?

Yes, contact Technical Service and request a protocol.

Can protein be obtained from RNA*later*-stored samples?

Yes, proteins are also preserved in RNA*later*. Storage in RNA*later* will denature proteins, therefore total protein obtained from samples stored in RNA*later* will be competent for applications such as Western blotting or 2D gel electrophoresis, but will not be suitable for applications that require native protein.

B. How to use RNA*later*

Use RNA*later* with fresh tissue only, do not freeze tissue before immersion in RNA*later*. Simply cut tissue samples to a maximum thickness of 0.5 cm in any 1 dimension, as long as samples are ≤0.5 cm thick, their size of the other dimensions is not important. Place the fresh tissue in 5 volumes of RNA*later*, and store as indicated for the desired temperature.

NOTE

Ambion offers RNAlater®-ICE (Cat #7030) as a salvage pathway to recover tissues that have already been frozen. RNAlater-ICE renders frozen tissues pliant enough for homogenization while maintaining low temperatures to protect the RNA from degradation.

1 TRI Reagent, and TRIZOL are registered trademarks of Molecular Research Center Inc.

Animal Tissue

RNA*later* does not dissolve or disrupt the structure of tissue samples, thus tissue that has been equilibrated in RNA*later* can be removed from the solution, sectioned into smaller pieces, and returned to RNA*later* if desired. Small organs such as rat liver, kidney and spleen can be stored in RNA*later* whole.

Plant Tissue

Many plant tissues can be simply submerged in 5 volumes of RNA*later* for storage. We have successfully isolated intact RNA from tobacco leaf explants, entire arabidopsis and alfalfa seedlings, and from potato shoot tips. Plant tissues that have natural barriers to diffusion such as waxy coatings on leaves will probably require disruption to allow RNA*later* access to the tissue.

Tissue Culture Cells

Pellet cells according to the protocol followed by your laboratory. Wash to remove the culture medium (e.g. with PBS). Resuspend the cells in a small volume of PBS, then add 5 to 10 volumes RNA*later*.

Blood and Plasma

White blood cells can be effectively preserved in RNA*later* when separated from the red blood cells and sera and treated as tissue culture cells. RNA*later* will preserve RNA in anticoagulated whole blood, sera, and plasma; however, it may be difficult to recover cells or viral particles by centrifugation due to the density of RNA*later*. See the RiboPure™ Blood Kit (Ambion Cat #1928) manual for specific instructions on use of RNA*later* with whole blood.

Bacteria

RNA*later* is bacteriostatic; although bacteria do not grow in RNA*later*, the cells remain intact. *E. coli* stored in RNA*later* for 1 month at 4˚C are intact and yield undegraded RNA.

C. Storage of Samples in RNA*later*

Storage at –80˚C

Recommended for archival storage. Incubate samples at 4˚C overnight, then remove them from RNA*later* before storage at –80˚C. For tisssue culture cells, do not remove the RNA*later*, simply freeze the whole solution. The cell types we have tested do not lyse when frozen at –80˚C in RNA*later*. Samples can subsequently be thawed at room temperature and refrozen without affecting the amount or the integrity of the recoverable RNA.

Storage at –20˚C

Recommended for archival storage. Incubate samples at 4˚C overnight, then transfer to –20˚C. Samples will not freeze at –20˚C, but crystals may form in the storage buffer; this will not affect subsequent RNA isolation. Samples can subsequently be thawed at room temperature and refrozen without affecting the amount or the integrity of the recoverable RNA.

Storage at 4˚C

Ambion sees no evidence of RNA degradation in samples stored at 4˚C for up to 1 month.

If Refrigeration is not Possible:

Place the samples in as cool an environment as possible. If ambient temperature is above 25˚C, incubate samples in RNA*later* on ice for a few hours if possible before storing at ambient temperature.

Storage at 25˚C

RNA isolated from samples stored at 25˚C for one week is intact. In our experience, RNA from samples stored at 25˚C for two weeks appears slightly degraded (marginally acceptable for northern analysis, but still of sufficient quality for nuclease protection assay or RT-PCR analysis).

Storage at 37˚C

RNA isolated from samples stored at 37˚C is intact after a 24 hour incubation, but is partially degraded after a 3 day incubation.

D. RNA Isolation from Material in RNA*later*

1. Removing Samples from RNA*later*

RNA*later* can be discarded down the sink with running water.

Tissue

Tissues that have been stored in RNA*later* should be removed from the storage solution with sterile forceps, and submerged in RNA isolation lysis solution. Tissue homogenization should be rapid once the tissue is in lysis/denaturation solution.

Cells

There are two options for isolating RNA from cells stored in RNA*later*, the RNA*later* can be removed, or the RNA can be extracted from the mixture of cells and RNA*later*.

- Removal of RNA*later*
  Our experience is that cells become much less fragile when stored in RNA*later* and can be centrifuged at high speed without lysis. We have successfully centrifuged cells at 5000 x g without loss. Since different cells may respond differently to this force, we suggest you try pelleting a non-valuable sample first to confirm that you can recover your cells this way. An alternative is to dilute the RNA*later* by 50% immediately before centrifugation with cold PBS (or other buffered solution) in order to reduce the density of the solution.
- RNA extraction from cells in RNA*later*
  Alternatively, we have used one-step disruption/extraction solutions (e.g. RNAwiz™, and TRI Reagent) to purify RNA from cells that have not been removed from RNA*later*. This can be done by adding ten volumes of the one-step solution to the cell mixture, and proceeding normally. When Ambion's RNAwiz™ is used in this way, it may be necessary to dilute the aqueous phase before the RNA precipitation step, see below for more information.

2. Tips for RNA Isolation

Glass fiber-based extraction

Using glass fiber filter-based RNA isolation kits, it may be necessary to use a centrifuge to push lysates through the filter as opposed to using a vacuum manifold.

One-step disruption/extraction solutions

When using one-step RNA isolation products such as TRIzol® (or TRI Reagent) on RNA*later*-preserved samples, occasionally the aqueous phase is cloudy. If this occurs, simply continue the procedure, following the manufacturer's instructions. Cloudiness of the aqueous phase does not affect the quantity or quality of the RNA obtained.

With Ambion's RNAwiz™, there may be a problem getting the aqueous phase to mix with isopropanol at the precipitation step because of RNA*later* carryover. If this occurs, simply add a mixture of 50% water, 50% isopropanol until the solution becomes clear and the two phases mix. The amount of water/isopropanol required will depend on how much RNA*later* was carried over; if the sample was mostly RNA*later*, as much as an equal volume may be needed.

E. RNA*later* Specifications

Quality Assurance: RNA*later* undergoes quality assurance testing to verify that its composition is invariant from lot to lot.

Safety: This product is a proprietary solution whose chemical, physical, and toxicological properties have not been thoroughly investigated. See the following MSDS for more information.

F. RNA*later*® Material Safety Data Sheet

Physical data	
Appearance and odor	clear liquid, slightly viscous
Boiling point	n / a
Solubility in H_2O	soluble

Fire and explosion hazard data	
Flash point	n / a
Flammable limits in air	n / a
Extinguishing media	water, CO_2, foam, dry chemical (Use any means suitable for extinguishing surrounding fire)
Special fire fighting	Wear self-contained breathing apparatus and protective clothing.
Fire / explosion hazards	Irritating and / or toxic gases or fumes may be generated by thermal decomposition or combustion.

Health hazard data	
Effects of overexposure	Acute overexposure may cause irritation to eyes, skin, and respiratory tract.
Emergency first aid	Flush affected area with copious amounts of water. Irrigate eyes and skin for ≥15 minutes. Contact physician if irritation occurs due to salt content.

Reactivity data	
Stability	stable
Incompatibility	n / a
Haz. Decomp. Products	n / a
Hazardous Polymerization	n / a

Spill or leak procedures	
If released or spilled	Ventilate area. Absorb spill with inert material. Place in container with a lid. Wash spill area after cleanup.
Waste disposal method	Dispose of according to federal, local and state regulations.

Special protection and precaution information	
Respiratory protection	Not expected to require personal respirator usage. (Use NIOSH approved respirator if necessary)
Ventilation	Not expected to require special ventilation
Precautionary labeling	none
Handling and storage considerations	Laboratory aprons and gloves. Do not store in aluminum or copper containers. Keep tightly closed in a cool, dry place.

Bio-sample Quality Control (QC)

Procedure:

Annually, sites will collect and process 2 Cell Preparation Tubes (CPT), and 2 PaxGene tubes utilizing volunteer blood. The CPT tubes will be processed as per study Standard Operating Procedure (SOP). Viable and non-viable cells will be aliquotted and stored at the site for a month. PaxGene tubes will also be stored for a month. The aliquots and PaxGene tubes will be shipped directly to Fisher BioServices for QC.

Fisher BioServices will conduct a cell viability QC check, and a cell count that will detail the number of viable and non-viable cells per aliquot sample of the CPT tubes. They will conduct an RNA extraction, and quality check on the PaxGene sample.

Blood Sample Collection, Processing, Labeling, and Storage

- Each site will identify a volunteer who will provide the blood samples for testing.
- Sites will provide their own blood drawing supplies.
- Sites may utilize the cryovials provided by the DCC.
- Sites will utilize their own labels for the PaxGene tubes.
- Sample processing of the 2 CPT tubes (for 3 cryovials of viable cells and 3 cryovials of non-viable cells) is to be done under sterile conditions, and in a certified Bio-safety cabinet (TC hood) following the blood collection SOP in the Manual of Operations, Version 1.4, Section 9.2
- Sites will need a cryo marking pen for the cryovial sample labels from the CPT tubes and for the PaxGene tubes.
- Cryovials and the PaxGene tubes are to be labeled prior to storage in the freezer.
- Using the cryo marking pen, write (on the frosted portion of the cryovial) the site ID #, date of draw, and the type of sample; non-viable cells or viable cells.
- The label for the PaxGene tubes should contain the following information; site ID # and date of draw.
- Once the cryovials and PaxGene tubes are labeled place them in a -80°C freezer until shipping.
- Sites must allow the cryovials and PaxGene tubes to be stored in the freezer for 1 month.

Packing and Shipping Process for QC samples

- Sites may utilize the shipping boxes used for shipment of frozen specimens for genetic shipping.
- The shipping will be conducted as stated in the MOO Version 1.5, Section 9.5.
- The DCC has created a manifest template to be completed by each site prior to shipping the samples.
- The sites will include one manifest in the shipping box, one is to be sent electronically to the repository (daniel.forero@thermofisher.com) and the DCC (a2all-monitors@umich.edu), and the site will retain one manifest for record keeping.

All sites must complete the blood draw and processing by Friday, September 20, 2013. Sites are required to store these QC samples for one month as they do with the study subject bio-samples. The sites will ship QC samples to Fisher BioServices on Monday, October 21, 2013. We want to be sure all bio-samples are stored for the same amount of time across all sites.

- Fisher BioServices will not communicate results to sites.
- The DCC will communicate the results to the sponsor and study sites.
- All samples will be destroyed by Fisher BioServices after extraction and quality check.

Shipping Manifest for QC Samples

Site ID #	Date of Draw	Number of PAXGENE Tubes	Number of Non-Viable Cells Aliquots	Number of Viable Cells Aliquots	Date of shipment	Courier Type	Tracking #

A2ALL-*Link* User Guide
Version 1.8
August 2, 2013

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1. Getting Started

1.1. Log In

Access the website. Enter your username, and the default password you were given and click the red arrow. If the username and password are incorrect or invalid, a red X will show next to the Login icon.

The system will require you to change your password the first time you log-in. Once you have changed your password, the system will log you out, and require you to log-in again with your new password.

1.2. Patient Name Key

The Patient Name Key unencrypts the Personal Health Information (PHI). You will be a given a default namekey by the system administrators. The first time you log-in you will be required to change your site's namekey. Once you have reset the namekey to a new key, DO NOT LOSE THE NAMEKEY. The Data Coordinating Center (DCC) does not have access to your key.

Only unencrypt the PHI when you need to, and when you are in a place where it cannot be viewed by people who are not associated with the study.

After you have changed the Namekey, when you log-in, you will be taken to the namekey page. If you do not want to unencrypt the PHI, do not enter the key and click the red arrow. If you do want to unencrypt the PHI, enter the namekey and click the save and continue icon.

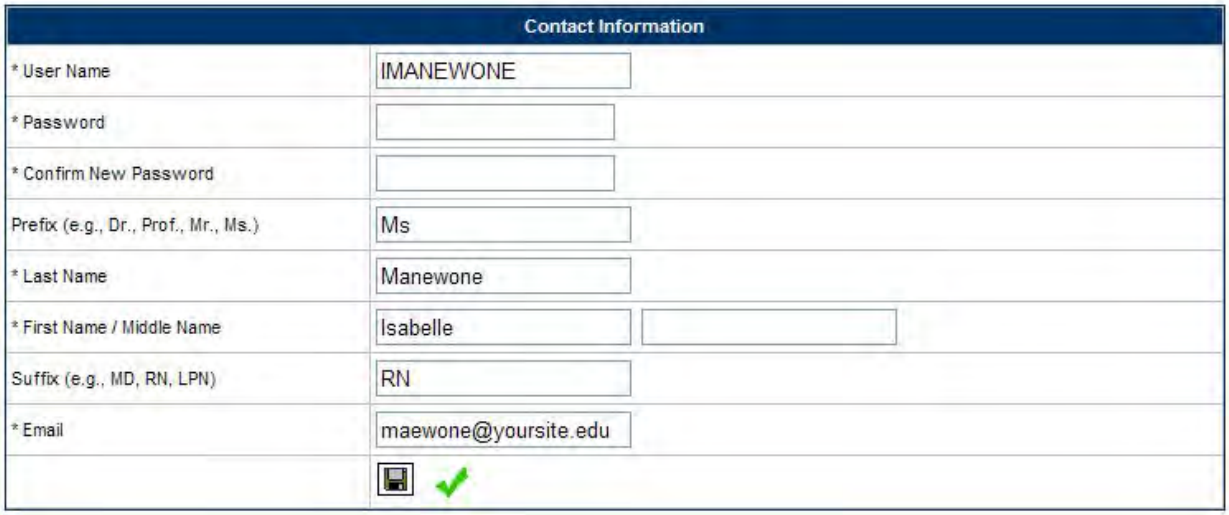
1.3. Adding Users/Creating a New Account

One staff member will be given the ability to create accounts by the DCC. After logging in as described above, click on the "My Account" Tab, then click on the "Add New Contact" link.

Figure 1 - Adding a New User

Assign a Username and Password. A good convention for username is to use the first initial and last name in capitals. Write down the username and password so you can remember it accurately when you give it to the new user. When s/he logs in for the first time, s/he will be prompted to change the password.

Figure 2 - New User Dialog Box



Click the "Save" icon when done. A green check will appear next to the icon indicating you've successfully added the new user.

To see a list of current users or to enable/disable a current user's privileges, return to the "My Account" tab and click the "Enable/Disable Users" link. You will see a list of active users. Check the "Enable" checkbox to restore or enable a user's privileges. Uncheck the "Enable" checkbox to disable a user's privileges.

1.4. Home Tab

The home tab shows unread announcements.

1.5. My Account

1.5.1. Contact Information

When you first log-in to the system, please review/update your contact information.

1.5.2. Change Password

If you wish to change your password, follow the link on the My Account tab.

1.6. Online Help

1.6.1. Documents

Here you will find study documents, including the Manual of Operations (MOO) and the protocol. As the DCC develops other documents that may be helpful, they will be uploaded to this area. Whenever a new

version of these documents is available, it will be uploaded, and an announcement will be sent to alert you to the new version.

1.6.2. Key to Icons

The Key to Icons provides an explanation for all icons you will encounter in the A2ALL-*Link* system. Please review these so you are familiar with them.

1.7. Announcements

All read and unread announcements can be found here. Once you have read an announcement, check the "Read" box and it will no longer display when you log-in. Your previously read announcements will be saved here in case you want to refer back to them later.

1.8. Contact Us

Use this email functionality to inform the Arbor-*Link* support team of a problem with the application or a question about functionality. The email goes to the Arbor-*Link* development team. Do NOT use this functionality to ask questions about interpretation of data fields or conduct of the protocol. Please refer to the MOO for guidance on who to contact with questions regarding those issues.

To send an email regarding a problem with the application, enter a brief descriptive phrase in the "Subject" box. Type your question or concern in the "Comments" box. You should expect a prompt response.

2. Subject List

2.1. Overview

If you are a continuing A2ALL site, your subject list is pre-loaded with all subjects from the Cohort Study who are eligible to be approached for enrollment into the Core Study. Donors are listed first, in order of subject ID, then recipients, in order of subject ID.

The left column shows the subject IDs and the subjects' names. The DCC doesn't know the names of your Cohort subjects, so the pre-loaded subjects' unencrypted name values are shown as "xxxx".

The CRF column is a link to a subject's event-driven eCRFs (Hospitalizations, SAEs, Complications, etc.)

The Subject Type column indicates whether the subject is a donor or recipient.

The Subject Consent Status column shows the subject's current consent status. For continuing sites, all pre-loaded subjects' consent status will be blank until you approach them and assign a new status (see Section 4).

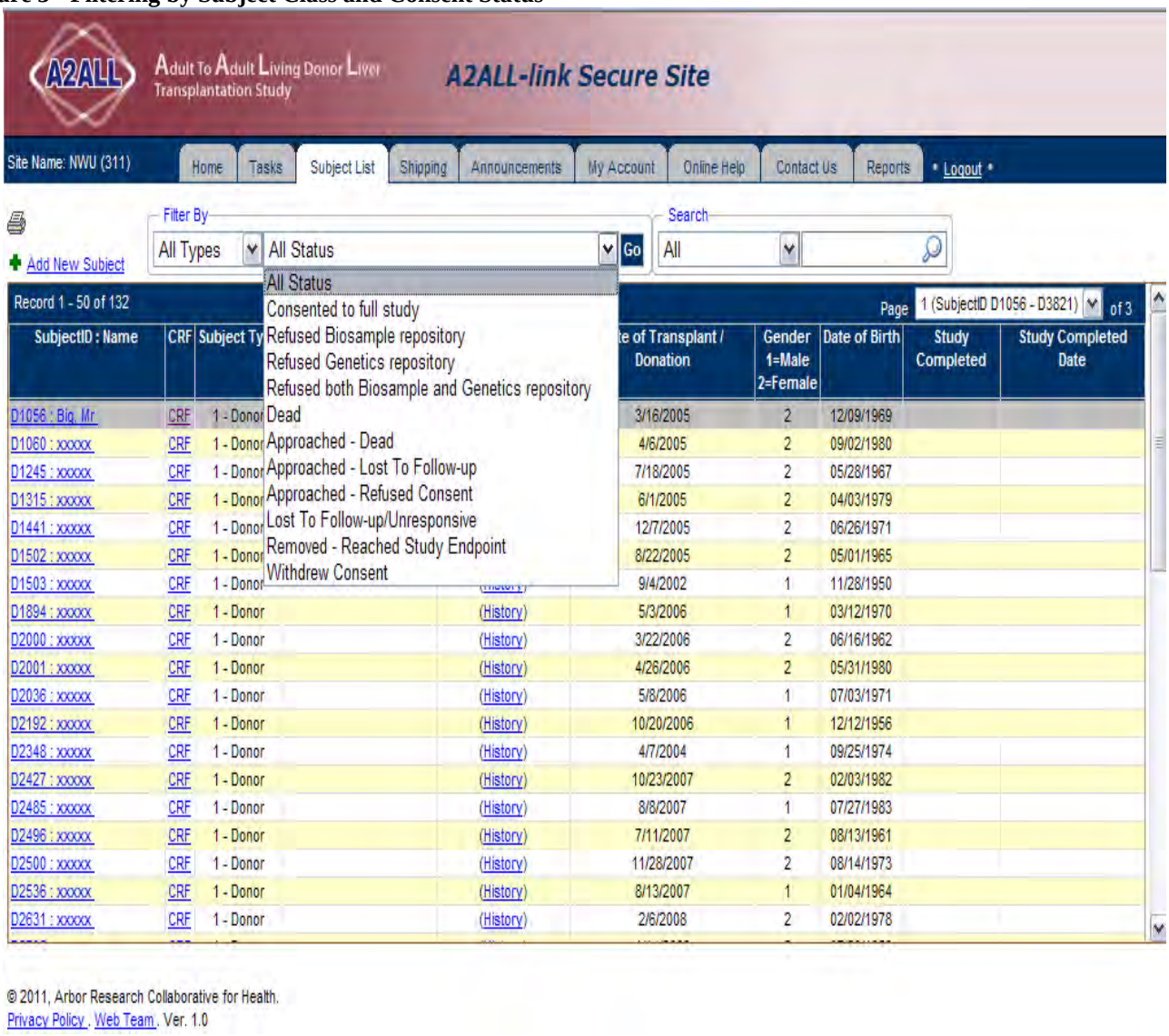
The Consent Status Date shows the date the subject's current consent status was established, and has a "history" link where you can review and edit the subject's consent status history.

There are additional columns that show the subject's date of surgery, gender, date of birth, additional study enrollment categories (HRQOL-Only and HCV only), whether the study is completed (a green check appears there), and the date the study is completed.

2.2. Filtering

In the "Filter By" box, you can filter by subject class, and consent status by operating the drop down boxes and selecting your filters, then clicking the "Go" button.

Figure 3 - Filtering by Subject Class and Consent Status



2.3. Searching

You can search by Subject ID, Subject Name (requires that the Name Key is entered) or both (ALL) by entering your search filter in the left box and your search criteria in the right box and clicking the magnifying glass. If searching by name, search by last or first name only, not both names.

Figure 4 - Enter Search Parameters

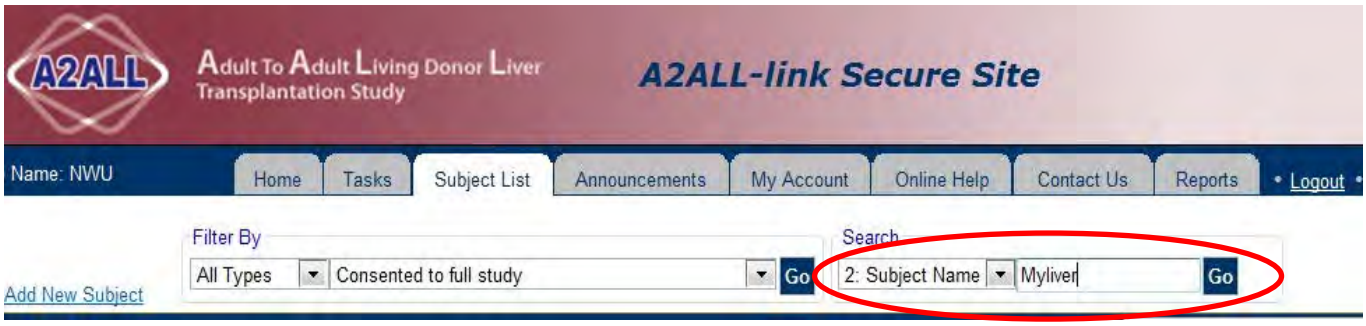
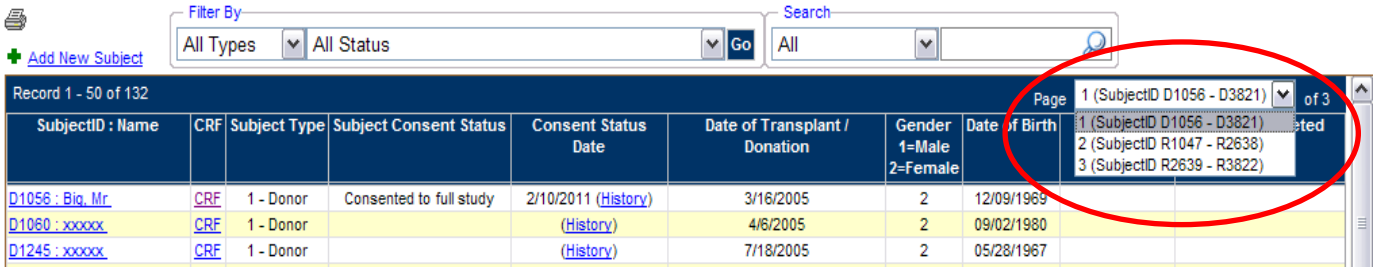


Figure 5 - Search Results Displayed

You can clear your search by clicking the red X next to your search parameter when the search results are displayed.

You can also sort the list by page. Note that the subject list grid has 50 lines. You can choose a page by the subject ID range.

Figure 6 - Paging through Subject List



2.4. Adding a New Subject

1. Click the "Add a New Subject" Link.
2. The Subject Dialog Box will open.
3. Enter the PHI and demographic information in the fields provided.
4. Enter the dates of TXP/Donation in fields provided.
5. THE PREFERRED METHOD OF MOVING THROUGH FIELDS IS TO USE THE TAB KEY!

6. The "Linked To" box connects donor and recipient pairs. Once one of the pair has been entered and saved into the system, when entering the other member of the pair, click the "Linked To" link and a list of possible subjects will appear. Choose the match and save.
7. If the subject is a donor and only eligible for the HRQOL Only sub-study (only open for "New" sites), click the check box that says "HRQOL Only". (*see Figure 7)*
8. If the subject is a recipient, and only eligible for the HCV sub-study, click the check box that says "HCV Only". *(see Figure 7)*
9. Click Save.

Figure 7 - Enter New Subject Info in the Dialog Box

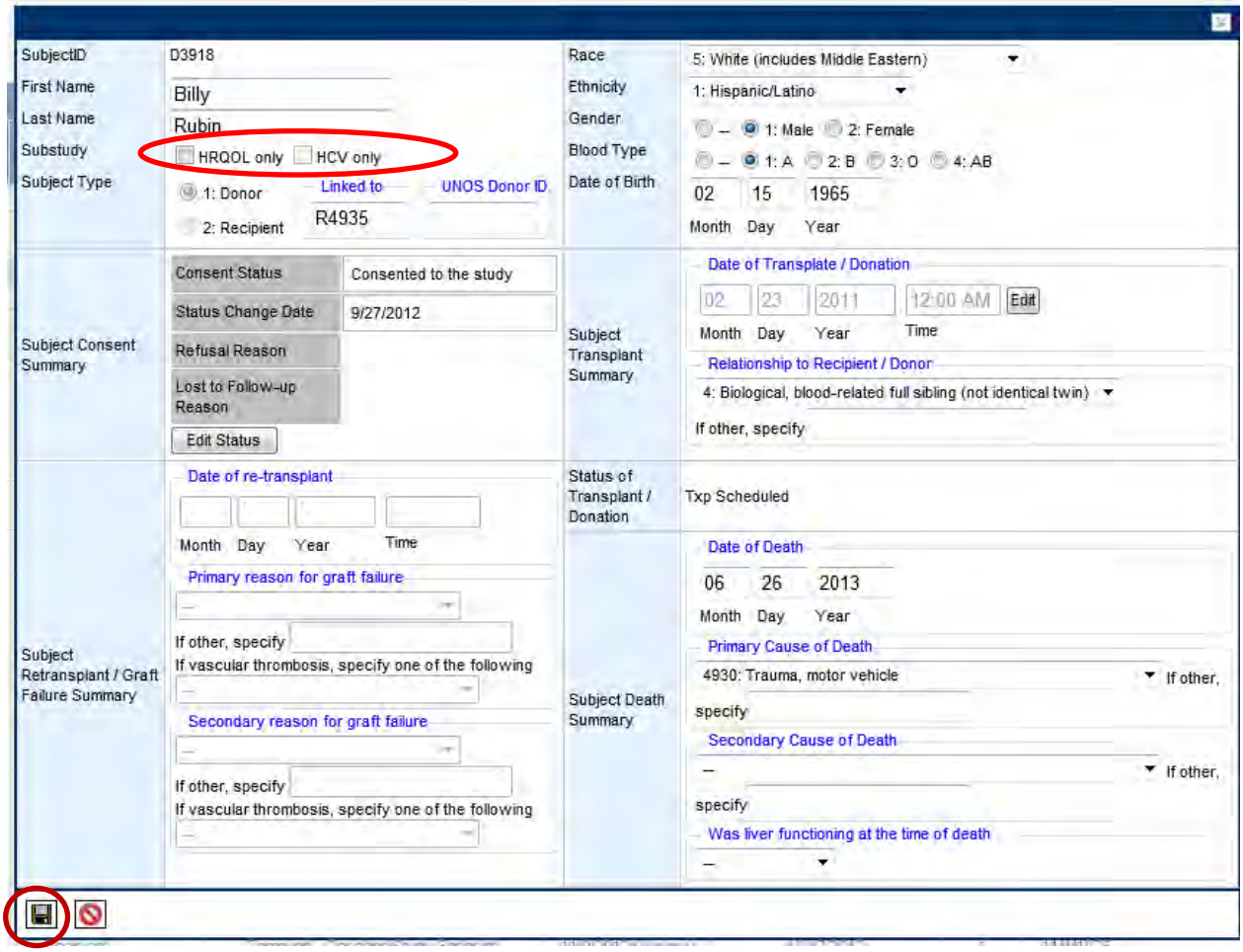


Figure 8 - The newly entered subject will appear in bold text on the last line of the Subject List

Record 1 - 50 of 132

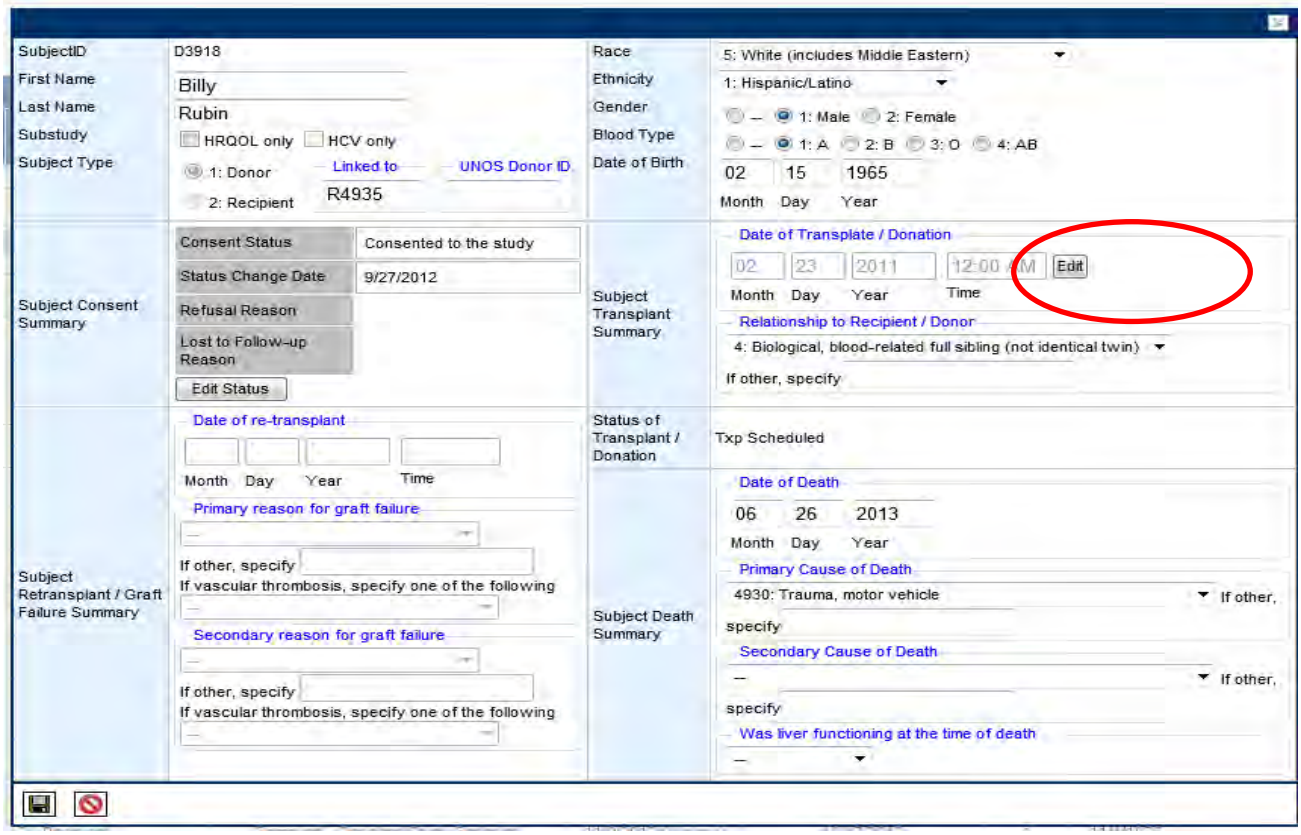
SubjectID : Name	CRF	Subject Type	Subject Consent Status	Consent Status Date	Date of Transplant / Donation	Gender 1=Male 2=Female	Date of Birth
D3575 : xxxxx	CRF	1 - Donor		(History)	6/5/2009	2	02/28/1964
D3797 : test, test	CRF	1 - Donor		(History)	2/1/2011	1	
D3799 : test2, test2	CRF	1 - Donor		(History)		2	05/05/1990
D3800 : test30, test30	CRF	1 - Donor		(History)			
D3801 : test4, test4	CRF	1 - Donor		(History)			
D3802 : test5, test5	CRF	1 - Donor		(History)			
D3803 : test6, test6	CRF	1 - Donor		(History)			
D3804 : xxxxx	CRF	1 - Donor		(History)	3/16/2005	2	12/09/1969
D3805 : O'Brien, Conan	CRF	1 - Donor		(History)	2/4/2011		
D3808 : Lobe, Lucy	CRF	1 - Donor		(History)	2/15/2011	2	12/09/1969
D3809 : Myliver, Miss	CRF	1 - Donor		(History)	5/16/2005	2	12/09/1969
D3812 : Quot, Ally	CRF	1 - Donor		(History)	9/10/2011	2	09/10/1900
D3814 : Kovach, Bill	CRF	1 - Donor		(History)	4/28/2011	1	05/29/1948
D3815 : Liver, Wanna	CRF	1 - Donor		(History)	12/9/2011	2	05/15/1970
D3818 : Columbo, Leonardo	CRF	1 - Donor		(History)	4/15/2011	1	01/25/1950
D3819 : xxx, xxx	CRF	1 - Donor		(History)			
D3820 : xxx, xxx	CRF	1 - Donor		(History)	2/1/2011	1	02/05/2011
D3821 : Smith, William	CRF	1 - Donor		(History)		1	
R3833 : Arie, Bill	CRF	2 - Recipient	--		03/15/2011	1	12/25/1969

2.5. Changing the Surgery Date

You can change the scheduled surgery date on any subject who has been prospectively entered (new Core subjects).

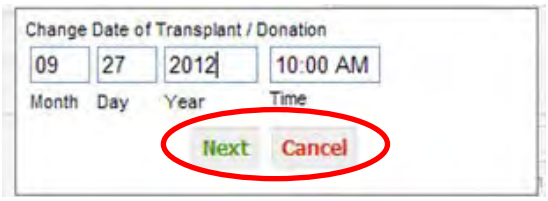
- Open the Subject Dialog Box, and click the "Edit" button next to the surgery date fields.

Figure 9: Editing the Surgery Date



- A small dialog box will show the current surgery date. Enter the new date, and time in the fields provided and click "Next" to proceed with changing the date or to click "Cancel" to revert back to the previously saved date.

Figure 10: Enter New Surgery Date



- Another dialog box will appear showing all changes in visit dates and sample collection validity that will occur if you proceed with the change, and gives the option to confirm the change or cancel it.
- If you had previously collected bio-samples as part of a pre-op visit, the application will tell you whether the samples you collected are still valid according to the protocol collection windows. If the samples are invalid, you'll need to discard them, unlink the barcodes (you'll need to contact the DCC for assistance with unlinking the barcodes at this point), and link a new set of labels for the newly collected samples.

Figure 11: Surgery Date Change Event Confirmation

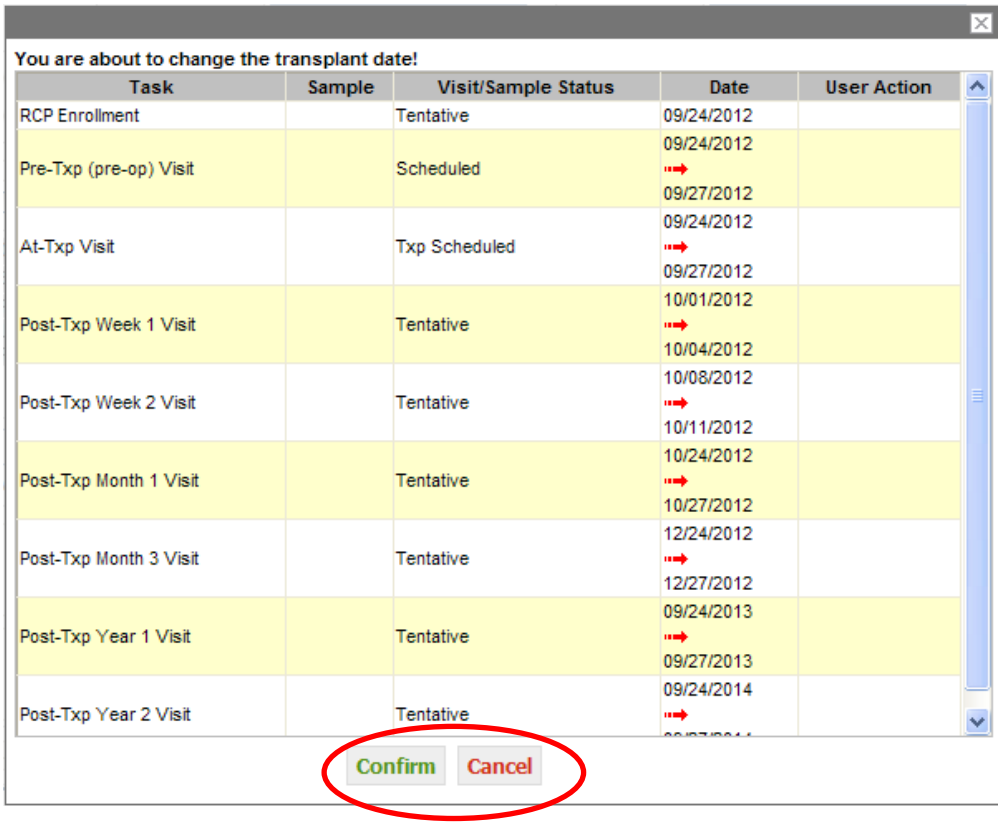


Figure 12: TXP Change Date Warning re: Sample Validity

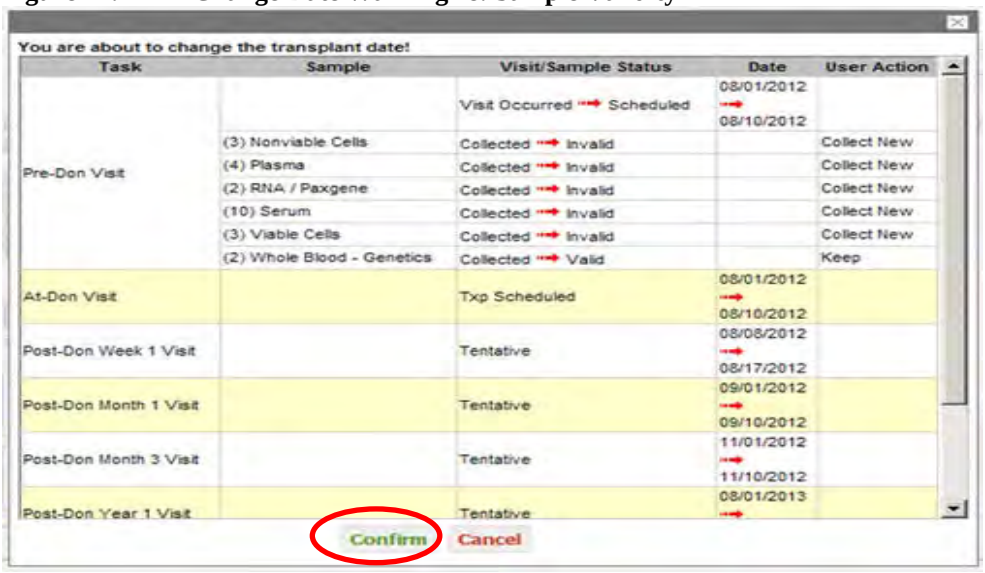
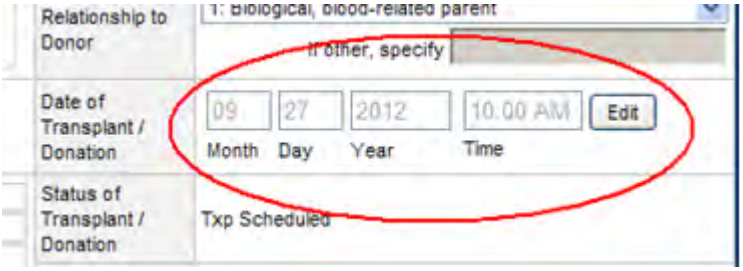


Figure 13: New Surgery Date Appears

- After clicking "Confirm", the new date will appear on the subject's registration screen.

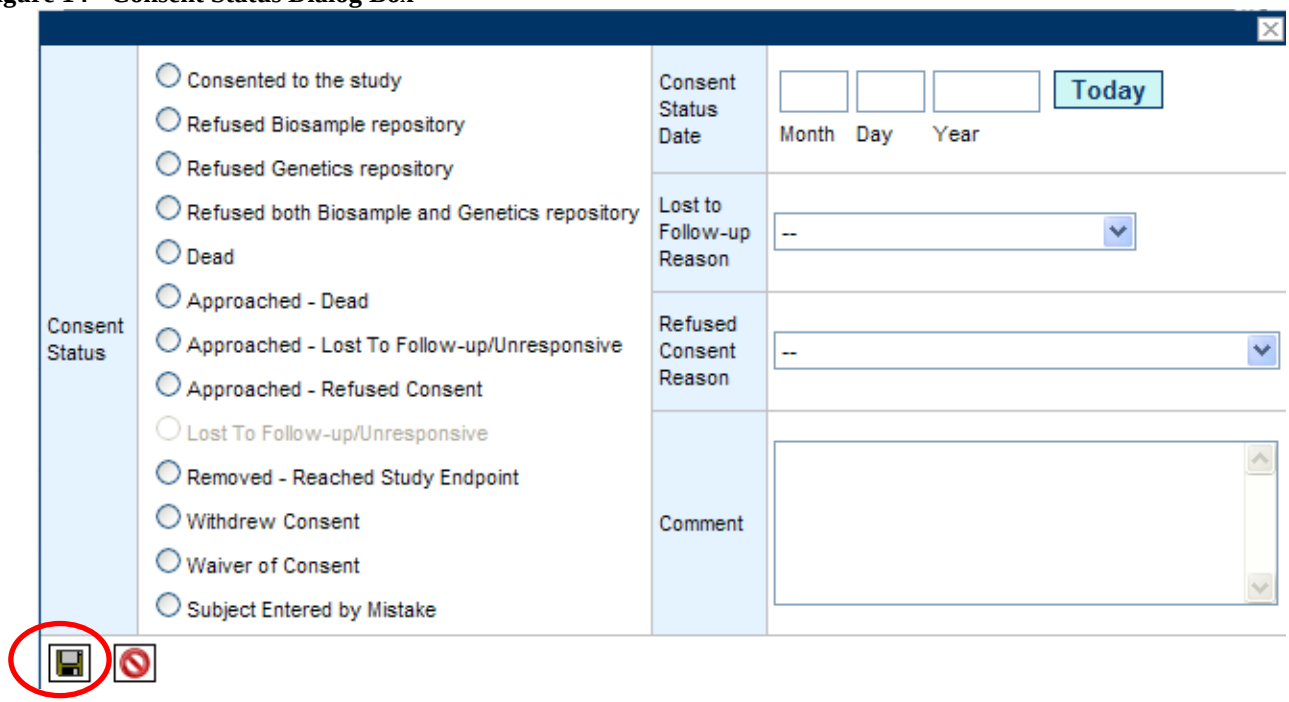


3. Establishing & Updating Consent Status

Whether your subject is a newly added subject, or a previous Cohort subject whom you have approached for consent, the process is the same (although the appropriate choices are different). Establishing and maintaining correct status is critical for how the application works. Choices that are displayed for eCRFs and events are all keyed off the consent status.

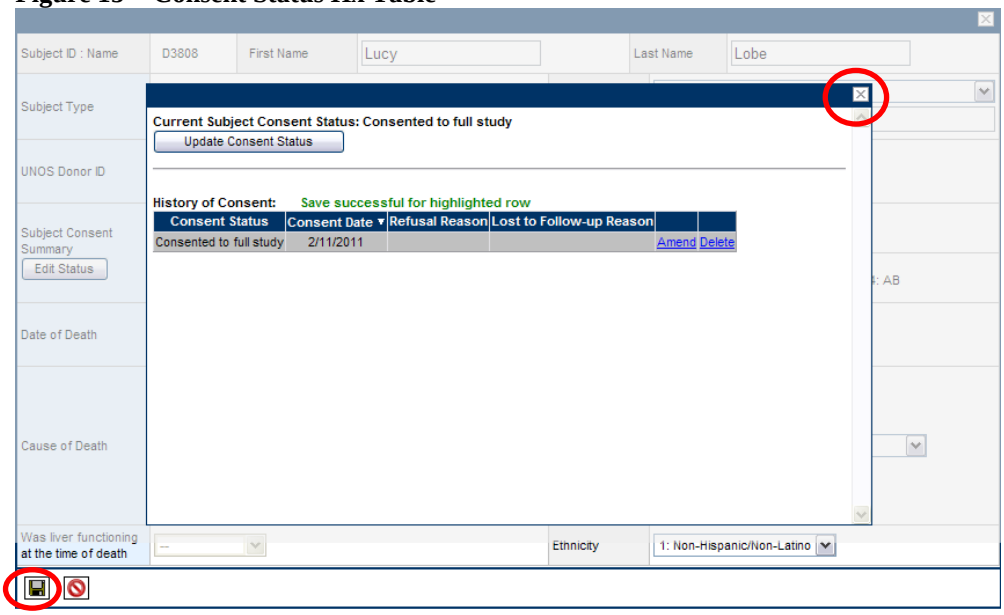
1. From the Subject List, click on the subject's ID/Name link in the left column. The subject dialog box will open.
2. Click the "Edit Status" button in the Subject Consent Summary box. The Consent Status Dialog box will open.
3. Click the "Update Consent Status" button in the Consent Status Dialog Box.
4. Choose the appropriate consent status. For definitions of consent statuses, please refer to the MOO.
5. Record the date of the consent status change (date consent was signed for consented subjects, date you knew about status change for non-consent).
6. You cannot choose "Lost to Follow-up/Unresponsive" until the subject has missed 3 consecutive visits which are documented.
7. Click the "Save" icon.

Figure 14 - Consent Status Dialog Box



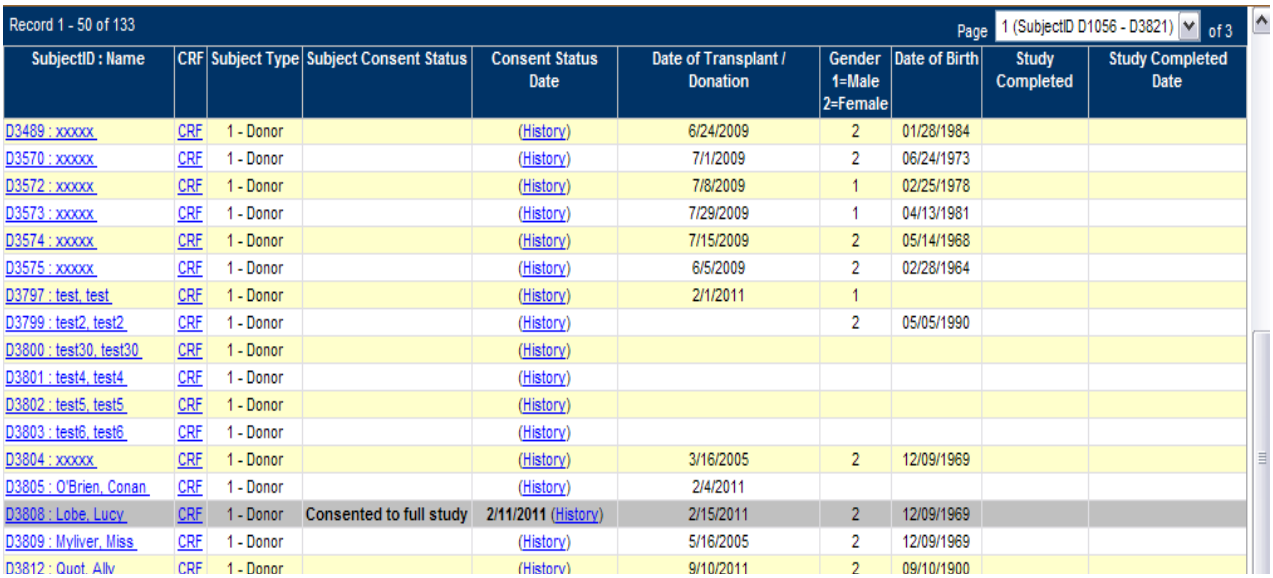
8. The page will refresh, and the new consent status will appear in the dialog box in the History of Consent table. Each time you add a new consent status, a new row will appear on the table.
9. If you made a mistake, use either the "Amend" or "Delete" links on the Consent Status Hx table, next to the erroneous status.
10. Do NOT use "Amend" or "Delete" to change a status that was previously true. Use "Update Consent Status" for that circumstance.

Figure 15 - Consent Status Hx Table



11. Close the Consent Update Dialog Box by clicking the X on the upper right corner.
12. You will be returned to the Subject Dialog Box. Note that the consent status now shows up on the Subject Consent Summary area.
13. Click the "Save & Close" icon.
14. Note that the newly documented consent status shows up as bold and is now visible on the subject list; along with the date of the consent status (usually will be the date of consent).

Figure 16 – Updated Consent Status and Status Date Appear on Subject Grid



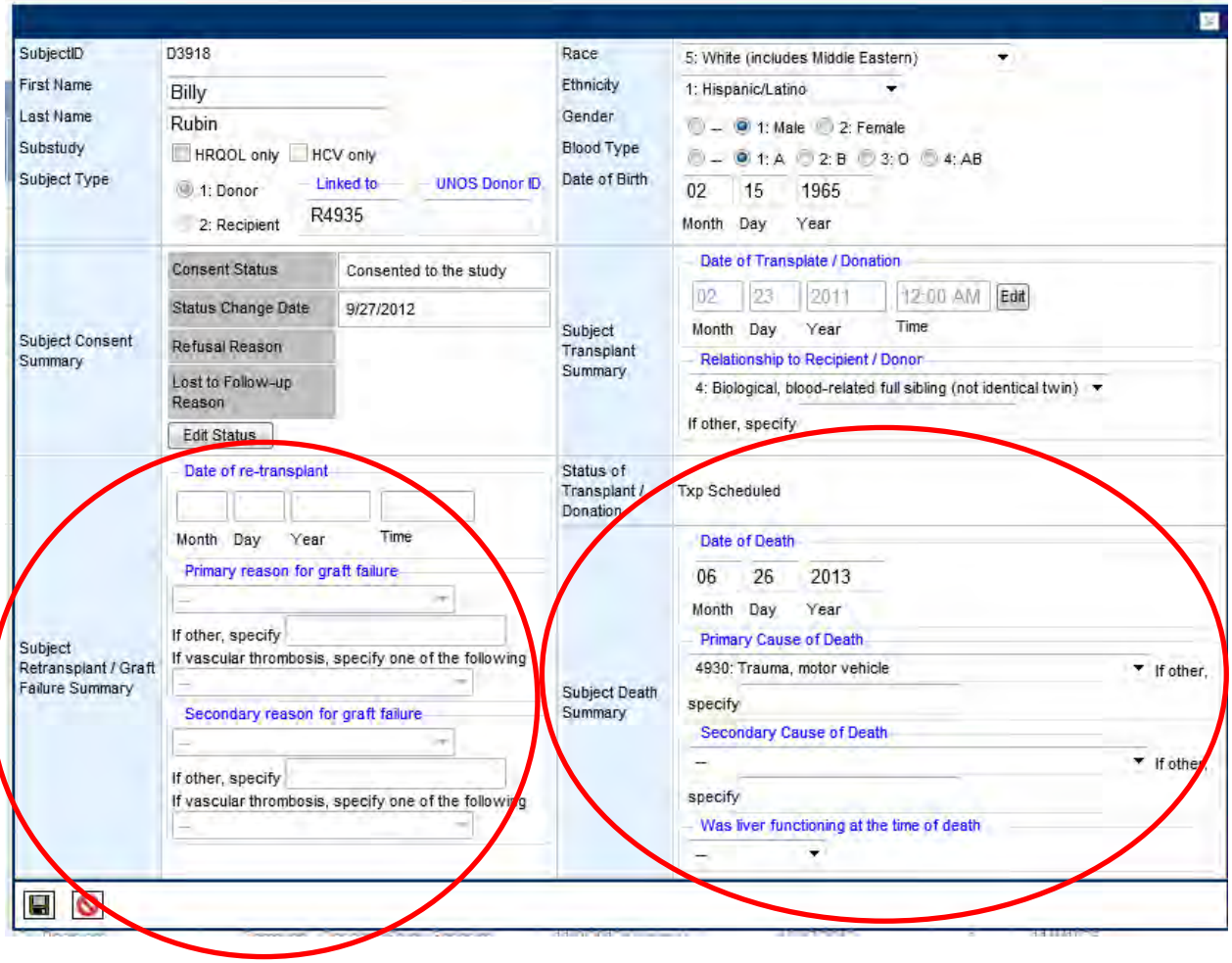
Record 1 - 50 of 133 Page 1 (SubjectID D1056 - D3821) of 3

SubjectID : Name	CRF	Subject Type	Subject Consent Status	Consent Status Date	Date of Transplant / Donation	Gender 1=Male 2=Female	Date of Birth	Study Completed	Study Completed Date
D3489 : xxxxx	CRF	1 - Donor		(History)	6/24/2009	2	01/28/1984		
D3570 : xxxxx	CRF	1 - Donor		(History)	7/1/2009	2	06/24/1973		
D3572 : xxxxx	CRF	1 - Donor		(History)	7/8/2009	1	02/25/1978		
D3573 : xxxxx	CRF	1 - Donor		(History)	7/29/2009	1	04/13/1981		
D3574 : xxxxx	CRF	1 - Donor		(History)	7/15/2009	2	05/14/1968		
D3575 : xxxxx	CRF	1 - Donor		(History)	6/5/2009	2	02/28/1964		
D3797 : test, test	CRF	1 - Donor		(History)	2/1/2011	1			
D3799 : test2, test2	CRF	1 - Donor		(History)		2	05/05/1990		
D3800 : test30, test30	CRF	1 - Donor		(History)					
D3801 : test4, test4	CRF	1 - Donor		(History)					
D3802 : test5, test5	CRF	1 - Donor		(History)					
D3803 : test6, test6	CRF	1 - Donor		(History)					
D3804 : xxxxx	CRF	1 - Donor		(History)	3/16/2005	2	12/09/1969		
D3805 : O'Brien, Conan	CRF	1 - Donor		(History)	2/4/2011				
D3808 : Lobe, Lucy	CRF	1 - Donor	Consented to full study	2/11/2011 (History)	2/15/2011	2	12/09/1969		
D3809 : Myliver, Miss	CRF	1 - Donor		(History)	5/16/2005	2	12/09/1969		
D3812 : Quot, Ally	CRF	1 - Donor		(History)	9/10/2011	2	09/10/1900		

4. Documenting a Subject Death and/or Date of Re-transplant/Graft Failure

1. Follow the steps provided in the previous section for updating a subject's consent status.
2. If the subject is a former Cohort subject, and you discover they've died as you've approached for consent, use the "Approached – Dead" status.
3. If the subject was consented to the Core Study and expired while in the study, use the "Dead" status.
4. In the Date of Status Change field, enter the date you discovered the subject's death. DO NOT ENTER THE DATE OF DEATH INTO THIS FIELD.
5. In the subject update dialog box, note that the Date of Death, Primary and Secondary Cause of Death, and Re-transplant and Graft Failure Summary fields are now active for you to fill in.
6. Enter the available information in the appropriate fields and click the "Save Icon" and close the Consent Status Update dialog box.
7. **Please inform the DCC of any donor deaths ASAP**. Do not use the email functionality in the A2ALL-*Link* application for this purpose. **Contact the Project Manager: Peg Hill-Callahan (Peg.Hill-Callahan@arborresearch.org).**

Figure 17 - Documenting Death and Re-transplant Information in Subject Dialog Box



5. Tasks Page

5.1. Overview

All study events and their associated tasks are managed from the Task Page.

The Task Page serves several purposes, including functioning as a calendar to help you manage study tasks. When you enter the date of transplant/donation in the Subject Dialog Box, A2ALL-*Link* calculates tentative dates for all post-operative study visits and populates those tentative dates on the Task List.

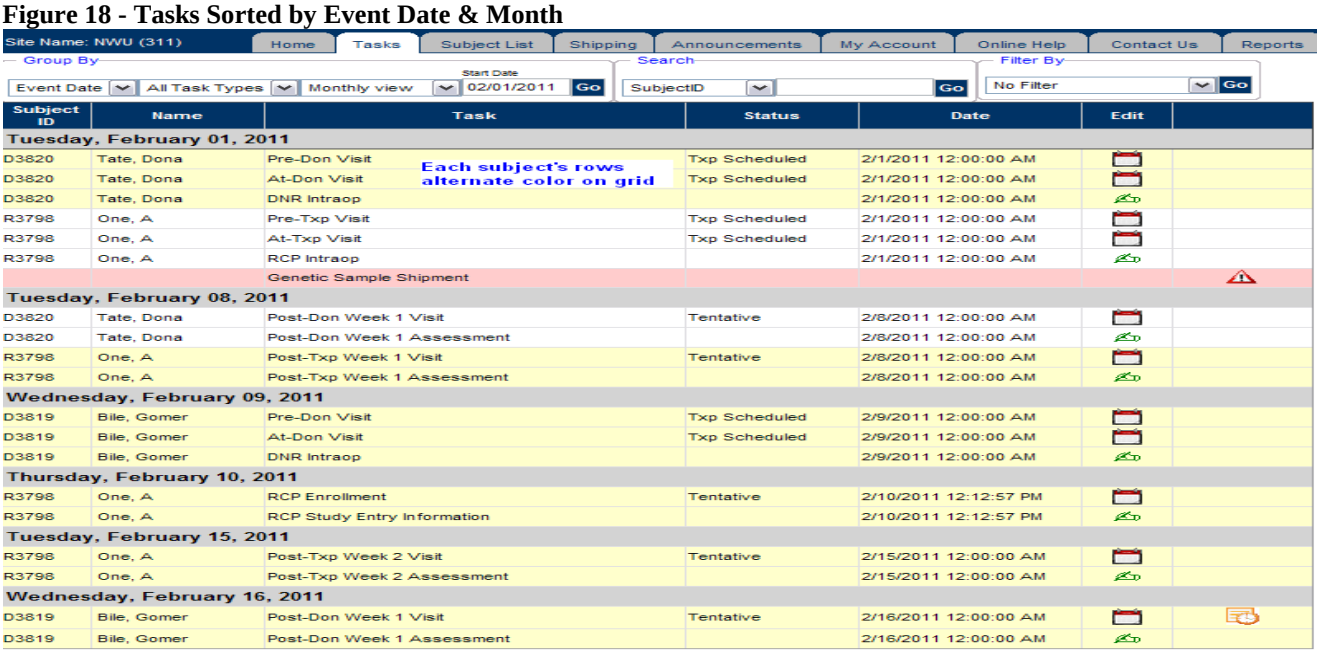
The Task Page appears as a grid/table. The far left columns show Subject ID and Name (note the name will be encrypted if the Name Key has not been entered).
The rest of the columns show tasks associated with that subject, their status, and the date associated with the status, an icon to edit the status and an information column that will show various icons depending on the task's status. Note that if there are tasks associated with more than one subject on a day, the rows associated with each subject have alternating stripes (yellow & white). From this page, you will schedule appointments, link sample barcoded labels to the subject and visit, and fill out visit-related eCRFs.

5.2. Group By

In order to manage tasks, you have several options regarding how to sort and view items on the Task Page. You can group by Event Date or Subject ID. You would use Event Date if you wanted an overview of tasks on a site-wide basis. You would use Subject ID if you wanted to view tasks sorted by Subject. You can then group further by choosing "Task Types" with the options of: all task types, visits, facility events, or eCRFs. Facility events are items such as Study Coordinator conference calls, or Sample Shipment dates.

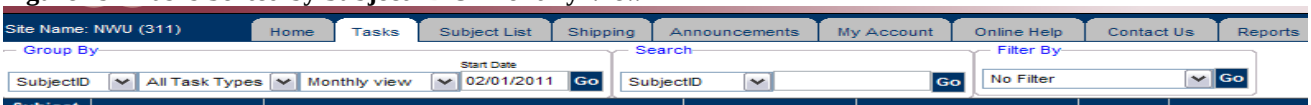
Once you have chosen how to group your view, then choose a time frame (weekly, biweekly or monthly) and a start date, and click "Go".

Figure 18 - Tasks Sorted by Event Date & Month



Subject ID	Name	Task	Status	Date	Edit
Tuesday, February 01, 2011					
D3820	Tate, Dona	Pre-Don Visit	Txp Scheduled	2/1/2011 12:00:00 AM	
D3820	Tate, Dona	At-Don Visit	Txp Scheduled	2/1/2011 12:00:00 AM	
D3820	Tate, Dona	DNR Intraop		2/1/2011 12:00:00 AM	
R3798	One, A	Pre-Txp Visit	Txp Scheduled	2/1/2011 12:00:00 AM	
R3798	One, A	At-Txp Visit	Txp Scheduled	2/1/2011 12:00:00 AM	
R3798	One, A	RCP Intraop		2/1/2011 12:00:00 AM	
		Genetic Sample Shipment			
Tuesday, February 08, 2011					
D3820	Tate, Dona	Post-Don Week 1 Visit	Tentative	2/8/2011 12:00:00 AM	
D3820	Tate, Dona	Post-Don Week 1 Assessment		2/8/2011 12:00:00 AM	
R3798	One, A	Post-Txp Week 1 Visit	Tentative	2/8/2011 12:00:00 AM	
R3798	One, A	Post-Txp Week 1 Assessment		2/8/2011 12:00:00 AM	
Wednesday, February 09, 2011					
D3819	Bile, Gomer	Pre-Don Visit	Txp Scheduled	2/9/2011 12:00:00 AM	
D3819	Bile, Gomer	At-Don Visit	Txp Scheduled	2/9/2011 12:00:00 AM	
D3819	Bile, Gomer	DNR Intraop		2/9/2011 12:00:00 AM	
Thursday, February 10, 2011					
R3798	One, A	RCP Enrollment	Tentative	2/10/2011 12:12:57 PM	
R3798	One, A	RCP Study Entry Information		2/10/2011 12:12:57 PM	
Tuesday, February 15, 2011					
R3798	One, A	Post-Txp Week 2 Visit	Tentative	2/15/2011 12:00:00 AM	
R3798	One, A	Post-Txp Week 2 Assessment		2/15/2011 12:00:00 AM	
Wednesday, February 16, 2011					
D3819	Bile, Gomer	Post-Don Week 1 Visit	Tentative	2/16/2011 12:00:00 AM	
D3819	Bile, Gomer	Post-Don Week 1 Assessment		2/16/2011 12:00:00 AM	

Figure 19 - Tasks Sorted by Subject ID & Monthly View



Subject ID	Name	Task	Status	Date	Edit
D3819					
D3819	Bile, Gomer	Pre-Don Visit	Txp Scheduled	2/9/2011 12:00:00 AM	
D3819	Bile, Gomer	At-Don Visit	Txp Scheduled	2/9/2011 12:00:00 AM	
D3819	Bile, Gomer	DNR Intraop		2/9/2011 12:00:00 AM	
D3819	Bile, Gomer	Post-Don Week 1 Visit	Tentative	2/16/2011 12:00:00 AM	
D3819	Bile, Gomer	Post-Don Week 1 Assessment		2/16/2011 12:00:00 AM	
D3820					
D3820	Tate, Dona	Pre-Don Visit	Txp Scheduled	2/1/2011 12:00:00 AM	
D3820	Tate, Dona	At-Don Visit	Txp Scheduled	2/1/2011 12:00:00 AM	
D3820	Tate, Dona	DNR Intraop		2/1/2011 12:00:00 AM	
D3820	Tate, Dona	Post-Don Week 1 Visit	Tentative	2/8/2011 12:00:00 AM	
D3820	Tate, Dona	Post-Don Week 1 Assessment		2/8/2011 12:00:00 AM	
R3798					
R3798	One, A	Pre-Txp Visit	Txp Scheduled	2/1/2011 12:00:00 AM	
R3798	One, A	At-Txp Visit	Txp Scheduled	2/1/2011 12:00:00 AM	
R3798	One, A	RCP Intraop		2/1/2011 12:00:00 AM	
R3798	One, A	Post-Txp Week 1 Visit	Tentative	2/8/2011 12:00:00 AM	
R3798	One, A	Post-Txp Week 1 Assessment		2/8/2011 12:00:00 AM	
R3798	One, A	RCP Enrollment	Tentative	2/10/2011 12:12:57 PM	
R3798	One, A	RCP Study Entry Information		2/10/2011 12:12:57 PM	
R3798	One, A	Post-Txp Week 2 Visit	Tentative	2/15/2011 12:00:00 AM	
R3798	One, A	Post-Txp Week 2 Assessment		2/15/2011 12:00:00 AM	

5.3. Search

You can search the Task List by Subject ID or Subject Name (you must have the namekey turned on to search by name). Note that you should only search by first or last name. Do not put both first and last name in the Search box. The Search box will only return tasks scheduled for that subject occurring in the time frame the Task List is displaying.

5.4. Filter By

You can filter the Task List (within the displayed time frame) for reminders, overdue, and no sample confirmation task statuses. All subject visits are calculated by the system based on the date of surgery entered into the Subject Dialog Box. These visit dates, and the visit statuses are viewed as "tentative". When a visit is in the ideal window, the reminder status icon  populates to remind you to schedule a visit for that time point. When you do that, the visit's status should be changed from "tentative" to "scheduled."

Overdue tasks show an icon with a triangle and an exclamation mark in it. 

Sample status (collected or not) is expected within 48 hours of a visit's occurrence. The icon shows on the last column as a red test tube.  For more information about icons, please go to the Online Help tab in the application.

5.5. Calendaring Function

By sorting by Event Date and choosing a timeframe (monthly, weekly, etc.), the resulting display allows you to view visits and tasks for the time frame, and assists you with planning your week, month, etc.

Figure 20 - Calendar View - Monthly

6. Study Visits

6.1. Pre-op Visits

When you enter the date of transplant/donation in the Subject Dialog Box, A2ALL-*Link* calculates tentative dates for all post-operative study visits and populates those tentative dates on the Task List.

The system places pre-operative visits tentatively on the same day as the operation. This gives you an easy way to find them so you can schedule the actual date.

6.1.1. Donor Pre-op Visits

For donors, the pre-donation visit task is to collect blood samples for the bio-sample repositories. This should occur no more than a week before the donation operation and can occur any time prior to the liver resection. Samples can be collected after the subject has received general anesthesia. Pre-op labs can also be drawn at this time. The results are recorded on the Donor Intraop eCRF.

The "At donation visit" is the donation operation, and the tasks associated with it are the collection of intraop Bx samples for the repository, and the collection of intraoperative data to be documented on the Donor Intraop eCRF.

6.1.2. Recipient Pre-op Visits

For recipients, the RCP Enrollment Visit is around the time of consent. The tasks associated with it are the collection of the genetic repository samples, and recording the lab results and other information on the RCP Study Entry Information eCRF.

The Pre-TXP visit is immediately pre-op (up to a week prior). The tasks associated with it are the collection of blood for the bio-sample repository and for pre-op labs (to be documented on the RCP Intraop eCRF).

The At TXP visit is the TXP operation, and the tasks associated with it are the collection of intraop Bx samples for the repository, and the collection of intraoperative data to be documented on the RCP Intraop eCRF. Samples for the At TXP visit can be collected after the subject receives general anesthesia.

6.2. Post-op Visits

Are calculated by the system and projected out as "tentative" based on the study visit schedule and date of transplant. All RCP subjects who are eligible for the HCV Sub-study will get a protocol biopsy and will have a HCV 3+ Years Post-op visit appear on the Task List when the subject is three or more years post-TXP, allowing you to schedule the biopsy and link labels for the bio-samples and microscope slides.

6.3. Visit Statuses

6.3.1. At TXP/Donation

For the TXP/Donation visit, the statuses are: (TXP/Donation) Scheduled, Aborted, Completed, and Postponed. If the status requires a date change, you must do that on the Subject Dialog Page.

6.3.2. All Other Visits

Visit statuses in A2ALL-*Link* are: tentative, scheduled, missed, visit occurred, and event occurred before site initiation. If a visit status isn't possible, given the subject type (i.e. prospective subject), then the invalid status won't appear in the drop down box. The system keeps track of all statuses assigned to a visit, and can be viewed by clicking the visit history link in the scheduling dialog box. The "event occurred before site initiation" status should be used for visits that A2ALL- *Link* generated (Gap subjects), based on the subject's date of transplant. These visits should have occurred prior to the date of consent.

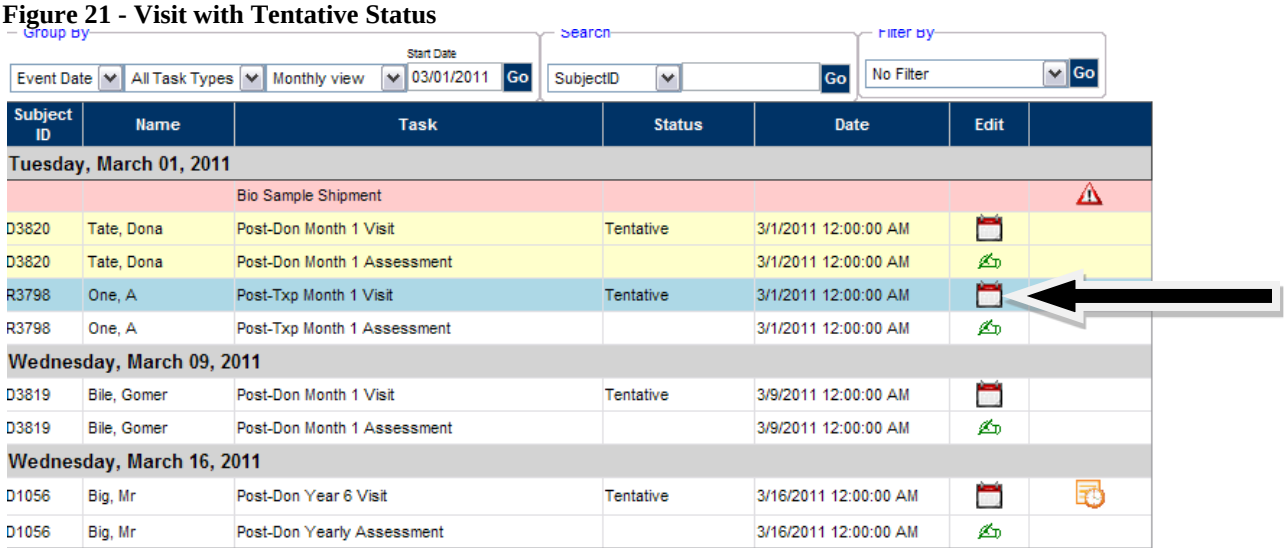
6.4. Task Completed Check-Box

The "task completed visit" status should be checked when all sample collection and visit eCRF data entry is complete.

6.5. Scheduling Visits

Once you have confirmed a visit date and time with a subject, go to the Task List and find the visit.

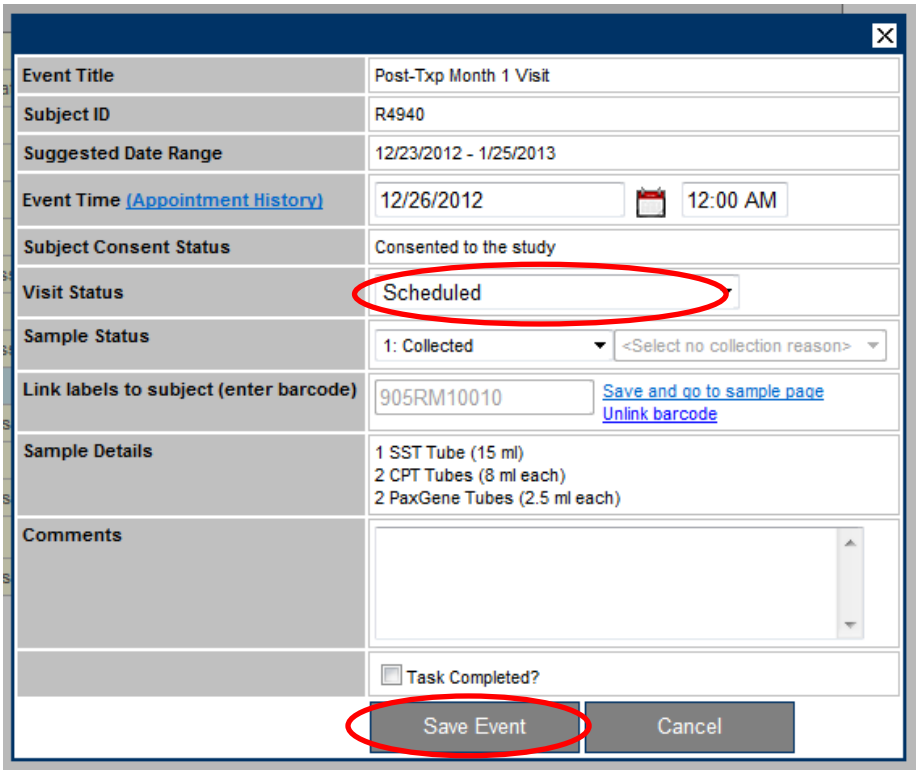
Figure 21 - Visit with Tentative Status



Subject ID	Name	Task	Status	Date	Edit	
Tuesday, March 01, 2011						
		Bio Sample Shipment				
D3820	Tate, Dona	Post-Don Month 1 Visit	Tentative	3/1/2011 12:00:00 AM		
D3820	Tate, Dona	Post-Don Month 1 Assessment		3/1/2011 12:00:00 AM		
R3798	One, A	Post-Txp Month 1 Visit	Tentative	3/1/2011 12:00:00 AM		
R3798	One, A	Post-Txp Month 1 Assessment		3/1/2011 12:00:00 AM		
Wednesday, March 09, 2011						
D3819	Bile, Gomer	Post-Don Month 1 Visit	Tentative	3/9/2011 12:00:00 AM		
D3819	Bile, Gomer	Post-Don Month 1 Assessment		3/9/2011 12:00:00 AM		
Wednesday, March 16, 2011						
D1056	Big, Mr	Post-Don Year 6 Visit	Tentative	3/16/2011 12:00:00 AM		
D1056	Big, Mr	Post-Don Yearly Assessment		3/16/2011 12:00:00 AM		

1. Click on the Calendar icon in the Edit Column. This will open the Visit Dialog Box.
2. Enter the scheduled date and time.
3. Change the visit status to "Scheduled".
4. Note the suggested range for the visit is displayed. This is an ideal range for a study visit to occur ±3months from "the tentative date displayed". A more "extended window" is allowed in the system ±6 months (for yearly assessments).
5. If you want to link the bar codes for samples to that subject and time point at the time you enter the scheduling information, please go to Section 7.1 for instructions.
6. Note that the subject's current consent status is displayed.
7. Note that the details for what tubes you will need for sample collection are also displayed.
8. If a subject has refused all sample collection, samples won't be expected, and the bar code link will not be active, and the sample details information will be blank.
9. Click "Save Event".

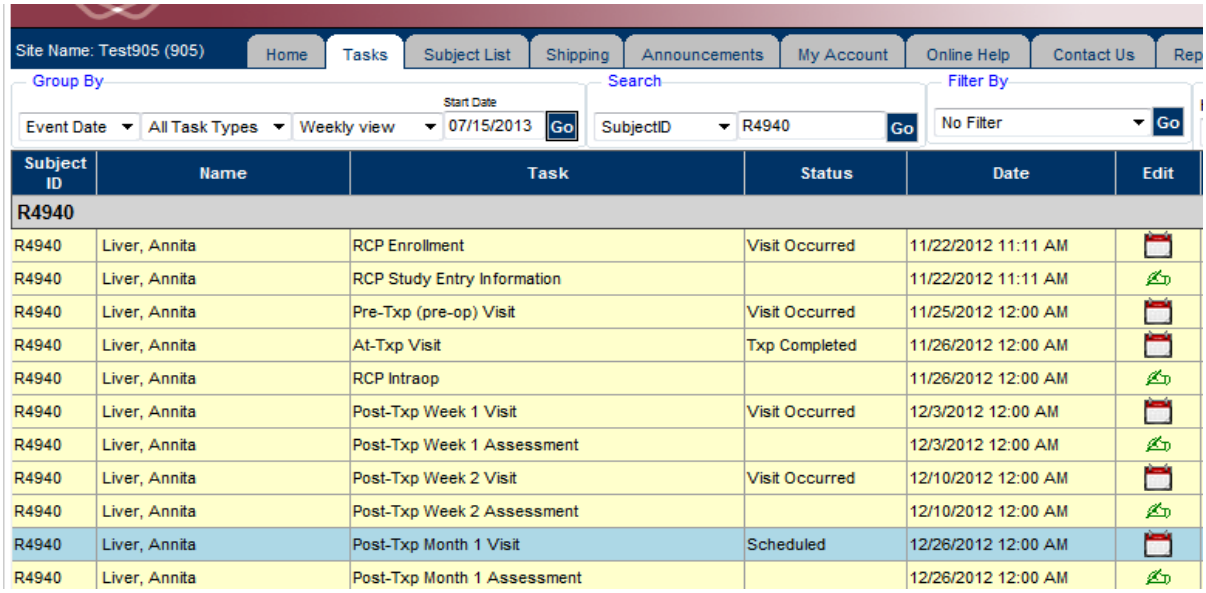
Figure 22 - Visit Scheduling Dialog Box



10. The visit will move to the appropriate date and its status will show as "Scheduled". Any eCRFs associated with that visit will also move to the new date. The newly scheduled appointment will be highlighted on the grid.

YOU HAVE 48 HOURS FROM THE TIME A SCHEDULED VISIT WAS SUPPOSED TO HAVE OCCURRED TO RECORD THE STATUS OF THE VISIT (MISSED or OCCURRED).

Figure 23 - Task List Showing Newly Scheduled Appointment



Subject ID	Name	Task	Status	Date	Edit
R4940					
R4940	Liver, Annita	RCP Enrollment	Visit Occurred	11/22/2012 11:11 AM	
R4940	Liver, Annita	RCP Study Entry Information		11/22/2012 11:11 AM	
R4940	Liver, Annita	Pre-Txp (pre-op) Visit	Visit Occurred	11/25/2012 12:00 AM	
R4940	Liver, Annita	At-Txp Visit	Txp Completed	11/26/2012 12:00 AM	
R4940	Liver, Annita	RCP Intraop		11/26/2012 12:00 AM	
R4940	Liver, Annita	Post-Txp Week 1 Visit	Visit Occurred	12/3/2012 12:00 AM	
R4940	Liver, Annita	Post-Txp Week 1 Assessment		12/3/2012 12:00 AM	
R4940	Liver, Annita	Post-Txp Week 2 Visit	Visit Occurred	12/10/2012 12:00 AM	
R4940	Liver, Annita	Post-Txp Week 2 Assessment		12/10/2012 12:00 AM	
R4940	Liver, Annita	Post-Txp Month 1 Visit	Scheduled	12/26/2012 12:00 AM	
R4940	Liver, Annita	Post-Txp Month 1 Assessment		12/26/2012 12:00 AM	

11. You can reschedule an appointment any number of times as long as it is still in the window. If a subject misses a visit and you re-schedule, you should save the event as "Missed", then go through the scheduling box again and enter the new appointment information.
12. You can view the appointment's history by clicking the history link in the dialog box.

7. Sample Collection, Documentation, and Shipping

This section details the sample functionality in the application and how to use it. For details about how to actually collect and process the samples, please refer to the MOO.

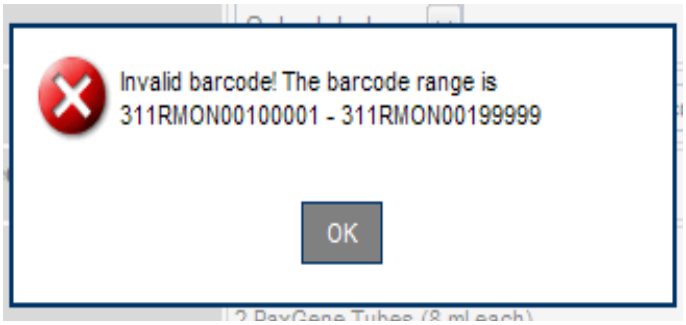
The DCC will produce rolls of barcoded labels by subject class and visit. You must link a roll of visit-specific barcoded labels to a subject.

7.1. Linking a Set of Visit Labels to a Subject

This can be done at the time you schedule a visit, or when a subject shows up for a visit. Select a roll of labels that matches the subject's class (Donor or Recipient) and the visit type.

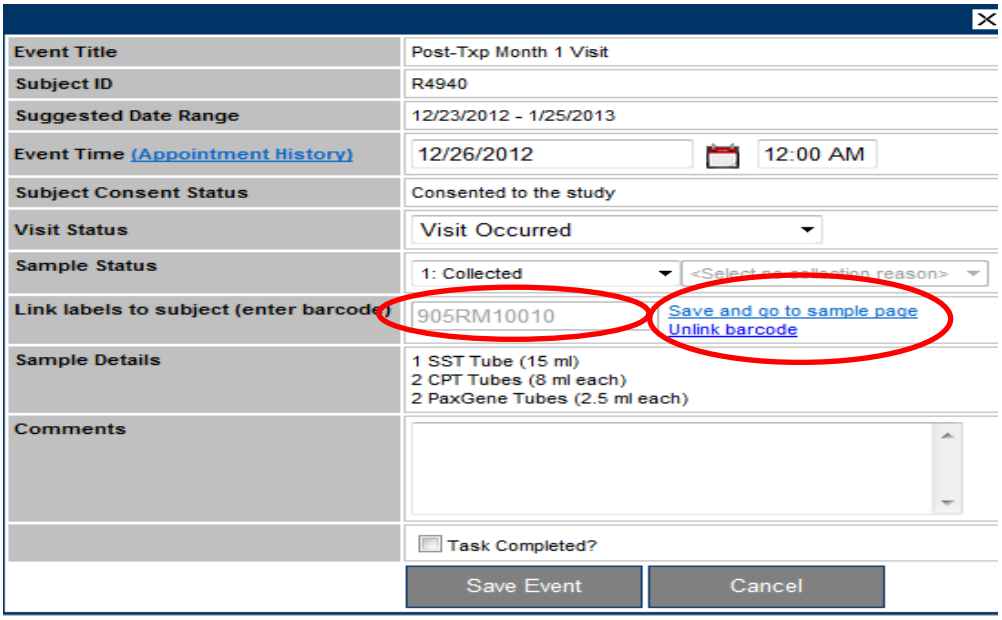
1. Open the Visit Schedule Dialog Box for the subject's visit.
2. Put your cursor in the "Link Labels to Subject (enter barcode)" field.
3. Scan the first label on the roll. Note that the system will not let you link a roll of labels that does not match the subject class, the visit type, or has already been linked to another subject.

Figure 24 - Bar Code Error Message



4. The human-readable bar code will appear in the window.
5. A "Save and go to Sample Page" link will appear next to the barcode number.

Figure 25 - Sample Bar Code Entered

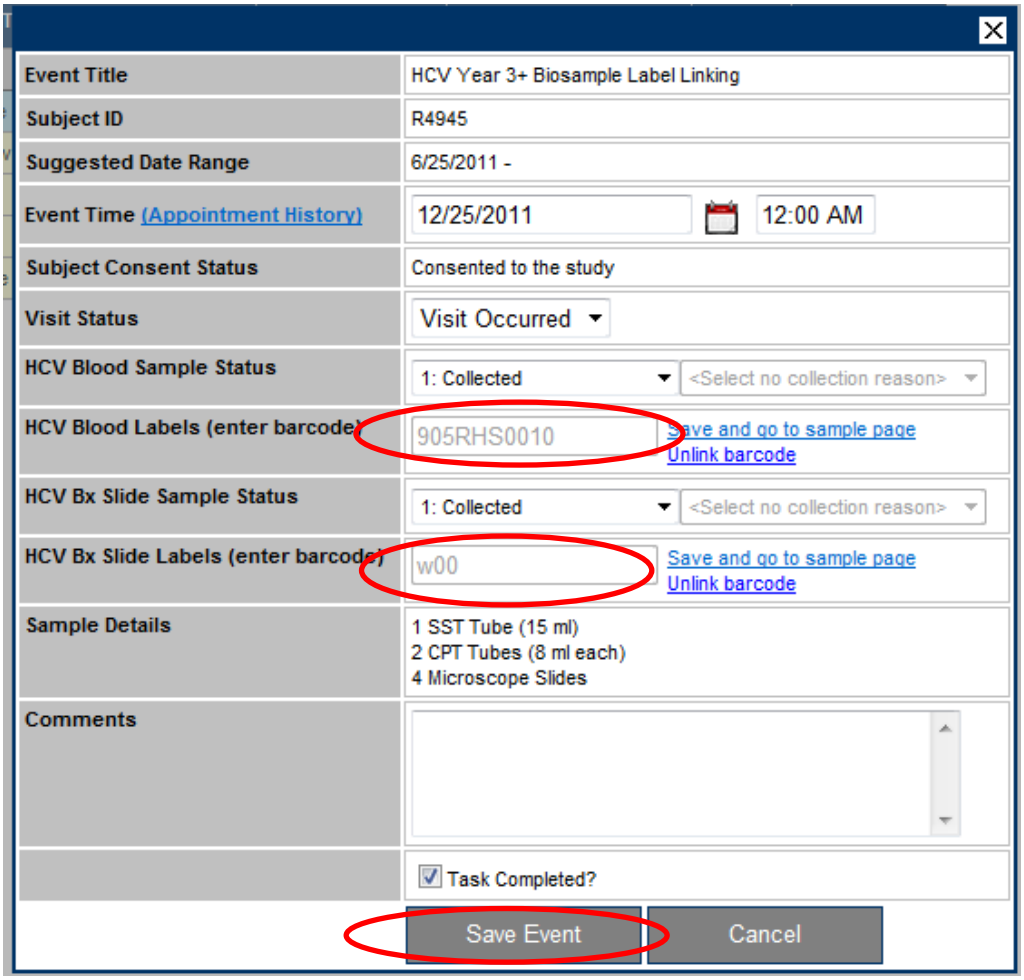


6. You can save the link by either clicking “Save Event” or the “Save and go to Sample Page” link.
7. Use the “Save Event” if you don’t wish to print your sample worksheet yet.
8. Click the sample page link if you want to print your worksheet.
9. MAKE SURE YOU HAVE A METHOD FOR KEEPING LINKED LABELS ASSOCIATED WITH THE CORRECT SUBJECT AND TIMEPOINT.
10. You will know you have successfully linked the labels when you re-open the visit window and see the barcode number grayed out, and an “Unlink Barcode” link visible. This is the only point you can “unlink” the labels if you discover you’ve linked the wrong labels to your subject.

7.1.1. Linking Microscope Slide Labels and Bio-samples for the HCV Sub-study RCPs, Post-Transplant Year 3 + HCV visit

- These biopsy slides include **only new biopsies** being collected for use for the HCV Sub-study, for the **HCV Year 3+ visit**. Biopsies collected within the past 12 months and older will be linked and recorded using the HCV past Biopsy slide label linking event described in Section 7.1.2.
- The visit scheduling window will generate when this option is selected in the HCV Study Subject Flow eCRF (Question B4 = Yes).
- The visit scheduling window has two linking boxes; one for bio-sample labels, and the other for microscope biopsy slide labels. HCV subjects obtaining a new HCV+3 year biopsy should have their bio-samples collected on the same date as the biopsy. For those HCV subjects who are not obtaining a new biopsy, collection of bio-samples only, will be documented on this +3 Year visit.
- The DCC will provide you with labels identified as “HCV Post-Transplant Year 3+ HCV visit.” These labels will be used for the collection of these bio-samples, and also for the collection of the +3 year new biopsy (if applicable).
- Link the labels as described above in Section 7.1, scanning into the windows provided for each type of sample. Proceed as described in Section 7.2 for printing out the label worksheets.

Figure 26: HCV Post-Transplant Year 3 + HCV visit, Slide Label Linking



7.1.2. Linking Microscope Labels for the HCV Sub-study RCPs, Past Biopsy Sample:

- These biopsy slides include:
  - biopsies completed within the past 12 months (protocol biopsy) of the HCV+3 year visit
  - past biopsies that either show cirrhosis (first biopsy with this diagnosis) and also the biopsy prior to this that didn't show cirrhosis (closest biopsy available that did not show cirrhosis). For this scenario, 2 past biopsy linking events will be added.
  - or the most recent biopsy collected, even if there is no cirrhosis and the most recent biopsy is past 12 months the biopsy slides are still needed.
- To obtain a past biopsy linking event, select the "Add a new Event" in the Tasks window (see Figure 27 below). You must select a subject from the drop down box and then select the green + icon (see Figure 28 below). This will generate a new scheduling window for the HCV Past Bx Sample (see Figure 29 below). Indicate the Date of the past biopsy in the event time data field.
- The DCC will provide you with labels, identified as "**HCV Past Biopsy Sample Labels".**
- Link the labels as described above in Section 7.1, scanning into the windows provided for each type of sample. Proceed as described in Section 7.1.3 for printing out the label worksheets.
- Select the biopsy slides collected on the sample collection page and save (Figure 31). This will generate the biopsy shipping manifest, (see Section 7.7).

- For collection of Bio-samples (with Amendment 3 consent), refer to Section 7.1.1 for instructions on label linking and sample documentation.

Figure 27: Adding a new HCV past biopsy sample event

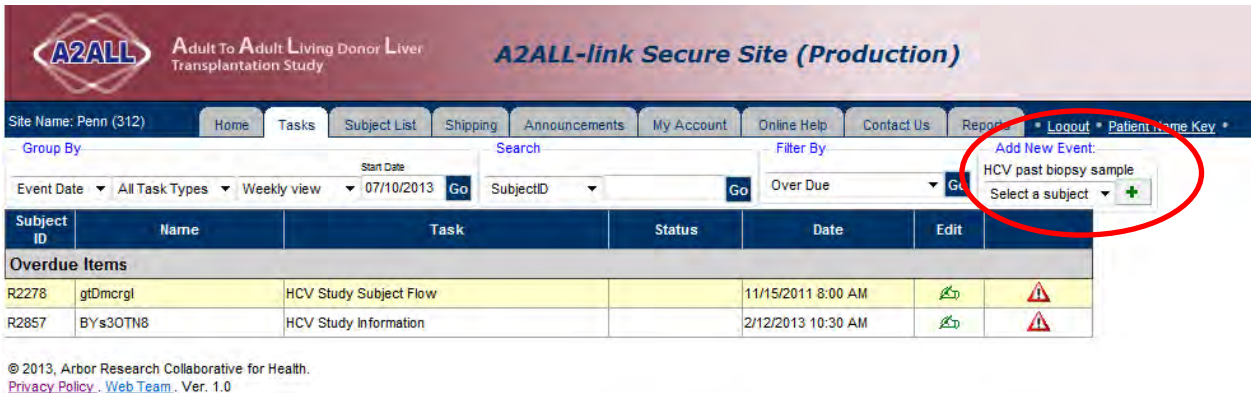


Figure 28: Selecting HCV biopsy subject (confirmation)

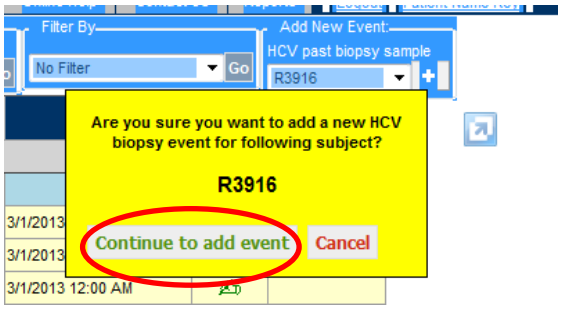
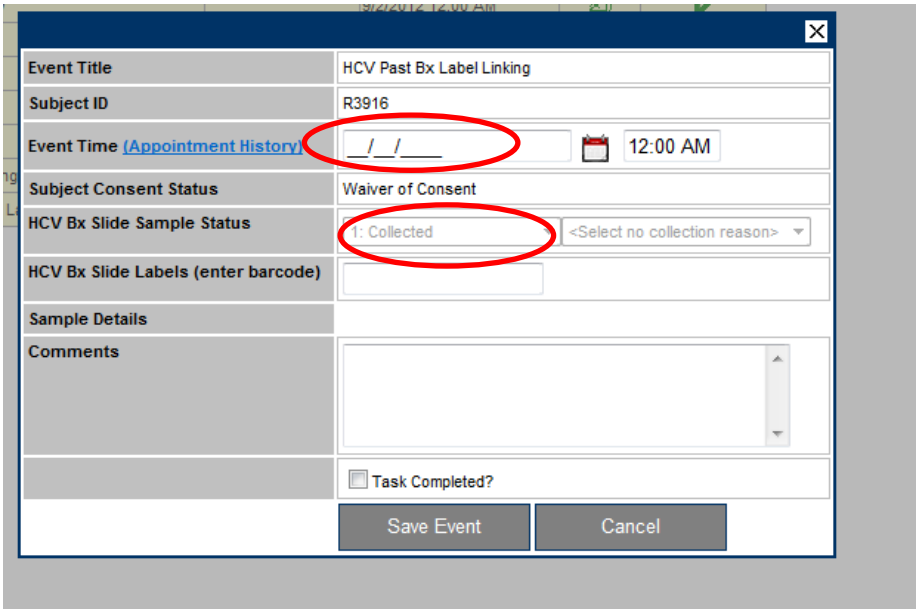


Figure 29: HCV past biopsy sample Label Linking Event



7.1.3 Printing a Label Worksheet

When you are ready to collect samples, you should print a label worksheet to take with you when samples are collected and processed. You should use this worksheet to document which samples were actually collected and stored (or discarded).

1. In the Visit Schedule Dialog Box, after linking the barcode to the subject (either immediately after scanning the first label when linking or by re-opening the dialog box after scanning the barcode and clicking "Save Event"), click the "Save and go to sample page" link.
2. You will be taken to a new page showing all possible labels for the visit. The label numbers match the labels on your roll.
3. Click the "Printer" icon on your Internet browser.
4. A label worksheet will print out. The subject's ID number, the visit type, and date will print on the top of the page.
5. After you have processed, aliquotted and labeled the samples, use the worksheet to indicate which labels were used and which were discarded. Once you've indicated which labels have been "used" or "discarded" you can't use the "unlink" labels function to correct any mistakes you may have made, this must be done by the DCC. Contact the DCC for assistance with unlinking of the labels.
6. This worksheet should be stored along with any extra labels, with the subject's source documentation for this visit.
7.

Figure 30: Sample Label Worksheet

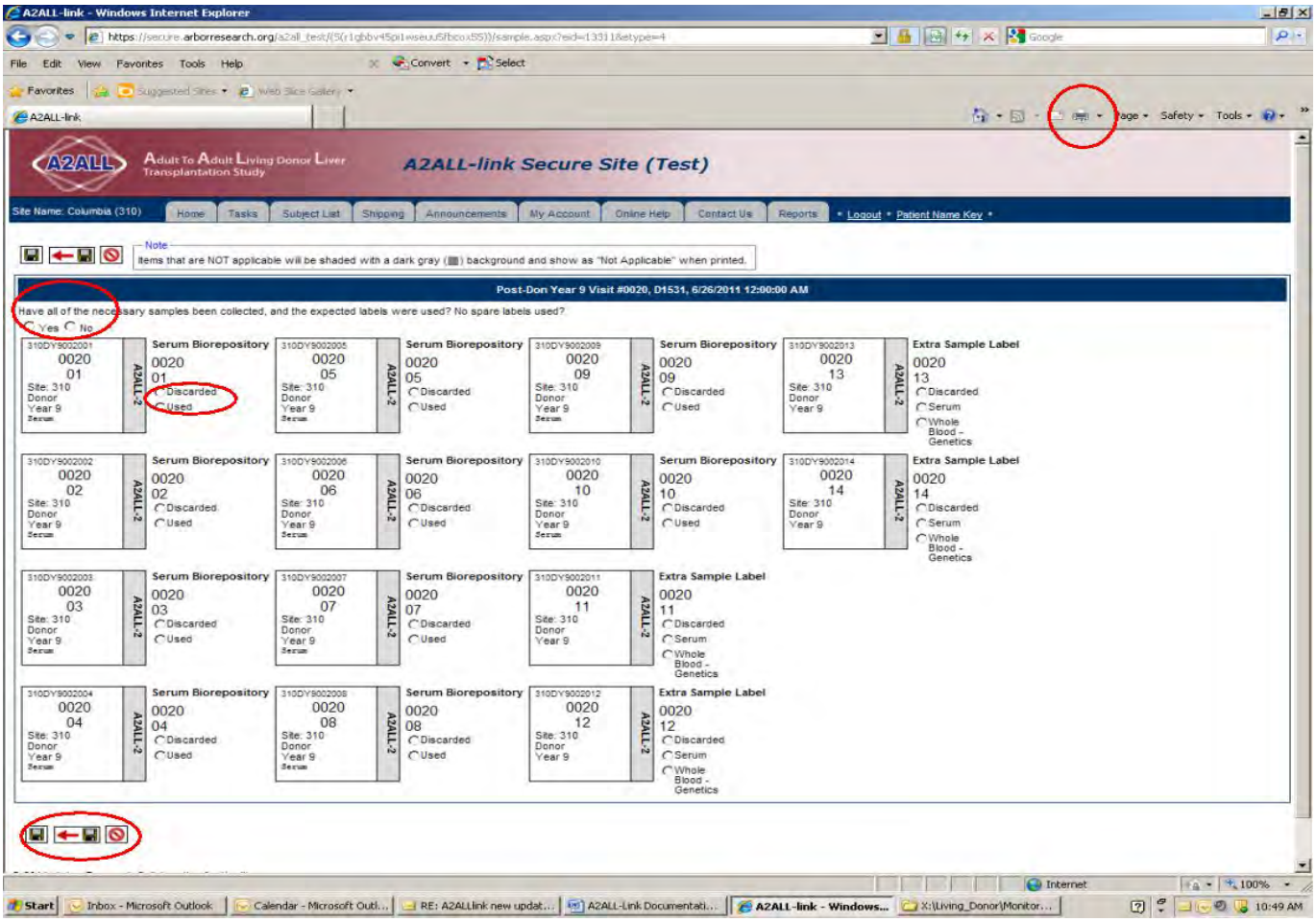
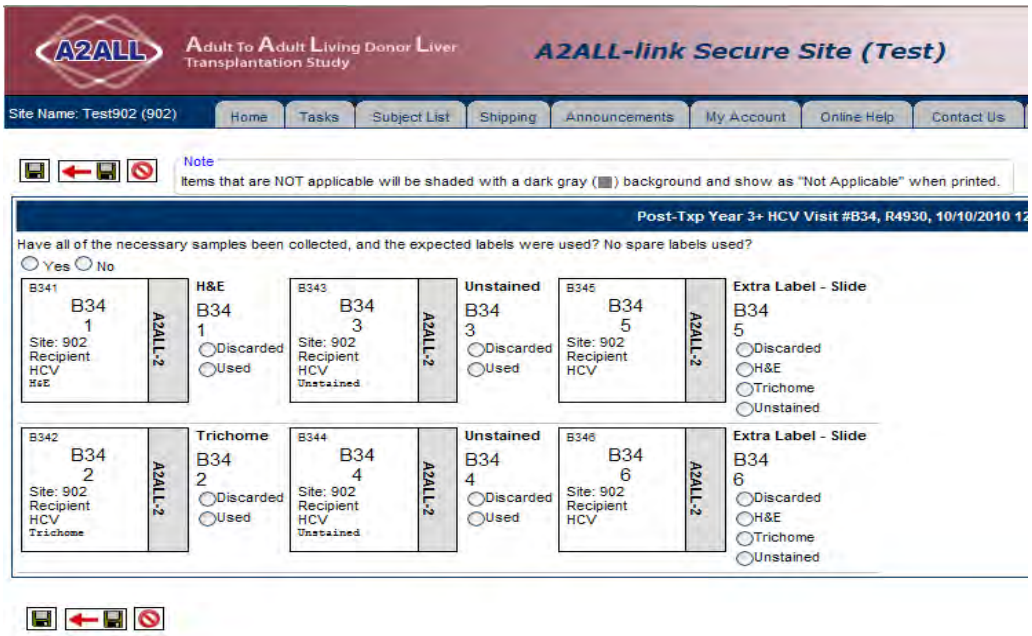


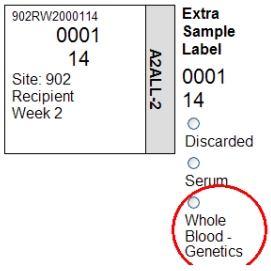
Figure 31: HCV Microscope Slides Label Worksheet



7.2. Genetics Samples

It is best to try to collect the Genetics Samples pre-operatively for prospective subjects. However, you can collect them at any time point for those subjects who are post-op. The genetics sample labels are available at all time points, as a choice you can designate for the extra labels. You should draw two 6ml EDTA tubes, utilizing two of the extra labels and clicking the "Whole Blood – Genetics" button.

Figure 32 - Extra Sample Label Detail



7.3. Sample Collection Documentation

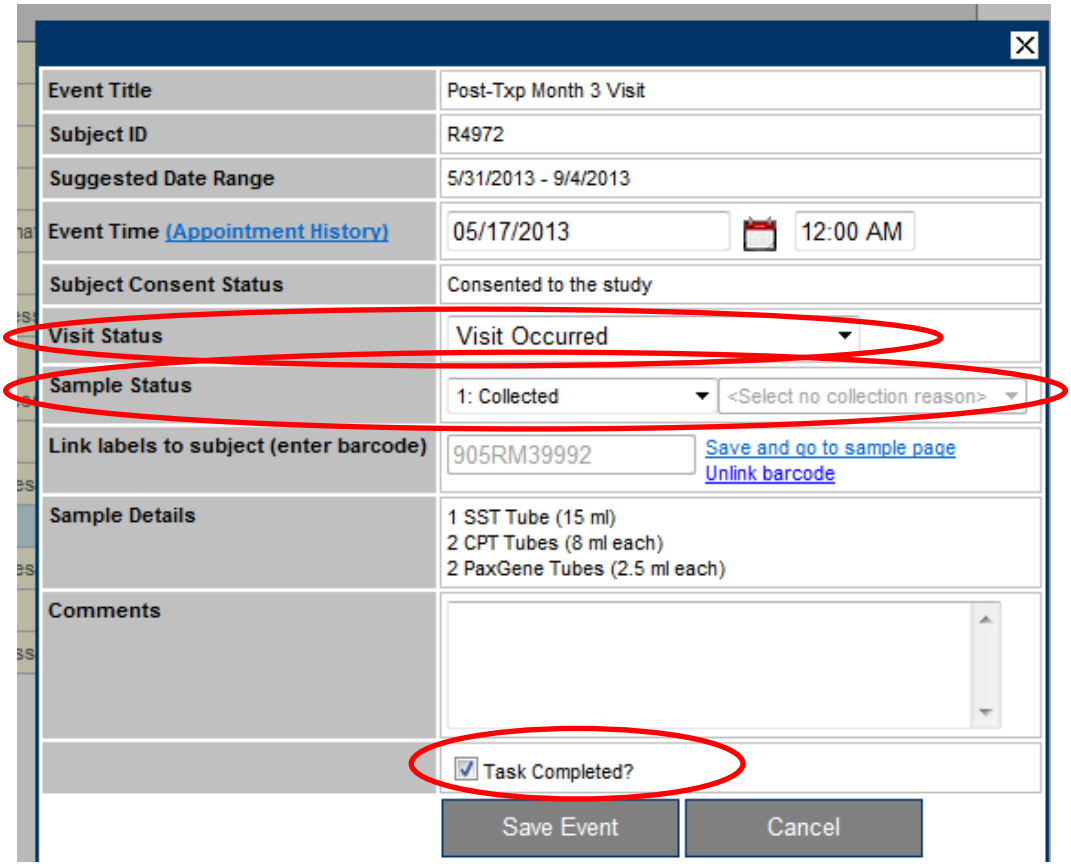
There are two levels of documentation associated with sample collection. The first level is confirming that the expected visit occurred. The second level is confirming the bio-samples were collected as expected at the expected visit. YOU HAVE 48 HOURS FROM THE TIME A SCHEDULED VISIT HAS OCCURRED TO ENTER THIS DOCUMENTATION INTO THE SYSTEM. If you do not enter the information within the required time, you will have an overdue warning associated with that visit.

We don't need to know the details of the sample collection at this point.

1. Go to the Visit Schedule Dialog Box for the appropriate visit.

2. Change the visit status to “Visit Occurred”.
3. Select the Sample Status (Collected or Not Collected). If “Not Collected” choose a reason. Administrative reasons are those associated with the study coordinator or the program. Subject refused is self-explanatory. Technical difficulties are reasons associated with the subject (couldn’t get a vein).
4. Collected means you collected at least one sample of those that were expected.
5. Click “Task Completed”.
6. Click “Save Event”.

Figure 33: Visit Scheduling Dialog Box – Visit and Sample Status



WITHIN A WEEK AFTER THE VISIT OCCURRED, YOU MUST DOCUMENT THE DETAILS OF THE SAMPLE COLLECTION (HOW MANY AND WHICH SAMPLES DID YOU COLLECT, PROCESS, AND LABEL).

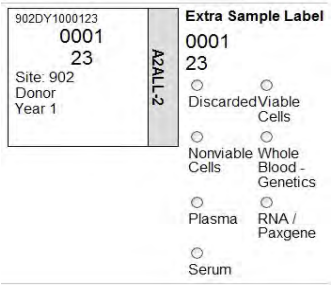
1. Make sure you have the correct sample label worksheet with you (see Section 7.2, Figure 30).
2. Go to the Visit Schedule Dialog Box for the appropriate visit.
3. Click the “Save and go to Sample Page” link.
4. If you collected, processed and labeled all expected samples, then click the “Yes” button after the, “Have all of the necessary samples been collected and the expected labels were used? No spare labels used?” (See Section 7.2, Figure 30).
5. All expected label statuses will change to “used.” Extra label statuses will change to “discarded”.

6. Editing will be locked.
7. If you did NOT use all of the expected labels, then check “No” to the question.
8. You will need to document the collection status of each sample by label.
9. Once you have documented the status of each label either by checking “yes” to all or on an individual basis, click either the “Save” icon or the “Save and Return” (to Task page) icon. (See Section 7.2, Figure 30).
10. If you skip documenting a label’s status, the system will not let you save your work. You must document a status (used or discarded for all labels on the page).
11. Once you’ve saved, you will **not** be able to utilize the “UNLINK BARCODE LABEL” function; you must contact the DCC for assistance.

7.4. Extra Labels

Each visit has four extra labels, in case you have an accident with one of the expected labels. If you use an extra label, you should mark “No” to the question at the top of the page. Click “discarded” for the expected label that won’t be used. Click what type of product you used the extra label for.

Figure 34: Extra Labels



7.5. Bio Sample Shipping

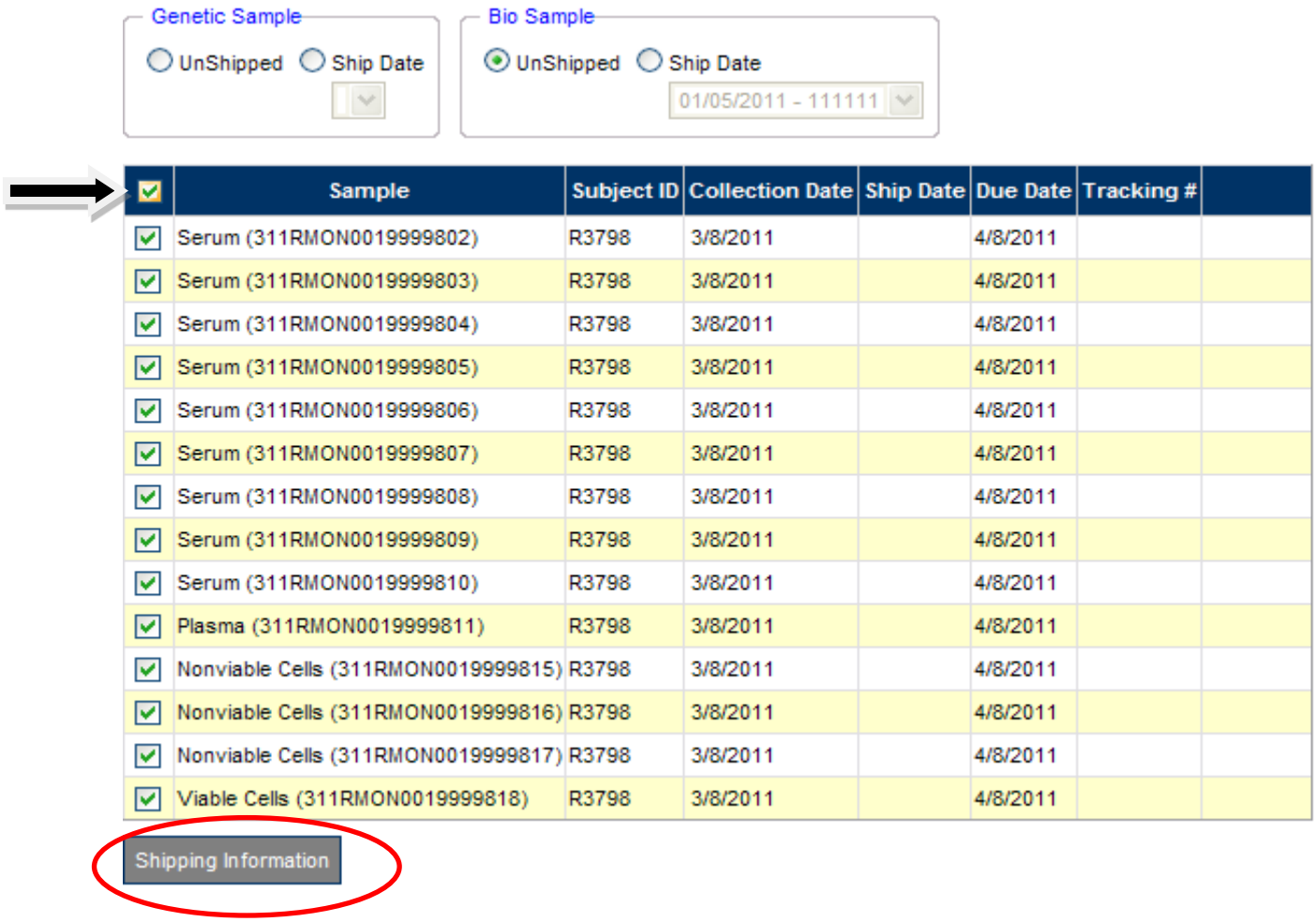
You must ship all Bio-samples to the NIDDK Bio-repository on a monthly basis; even if you only have a few samples. All samples from your freezer must be shipped monthly, according to your sites shipping schedule.

1. Click the “Shipping” tab.
2. On the Bio-sample side of the page, click “Unshipped”.

Figure 35: Shipping Tab View

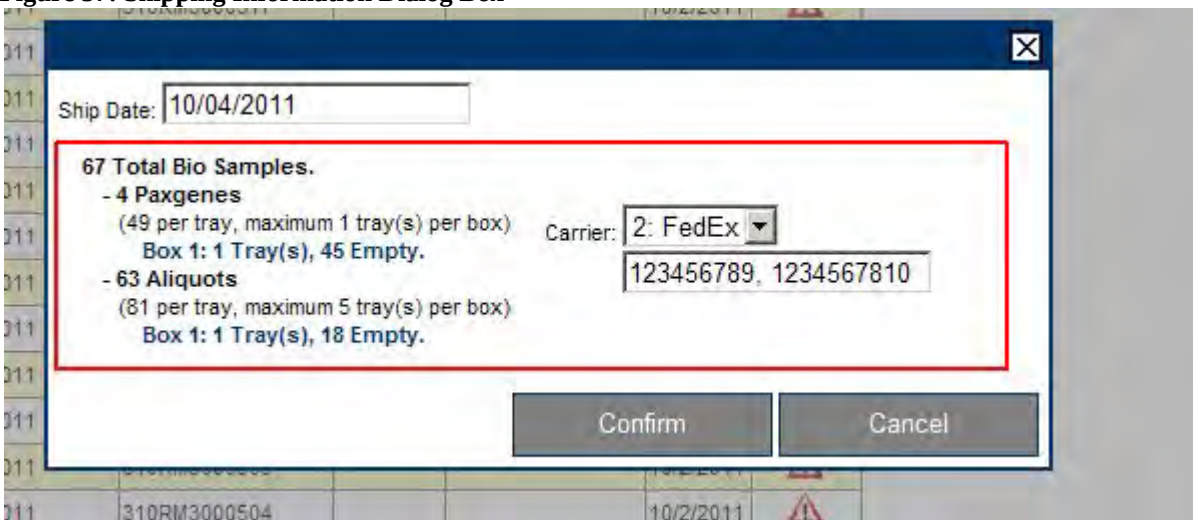
3. A list of all unshipped samples will be generated. For almost every instance, you should select “All” by clicking the box on the header row in the first column. This will check all of the samples on the list.

Figure 36: Samples to be Shipped List



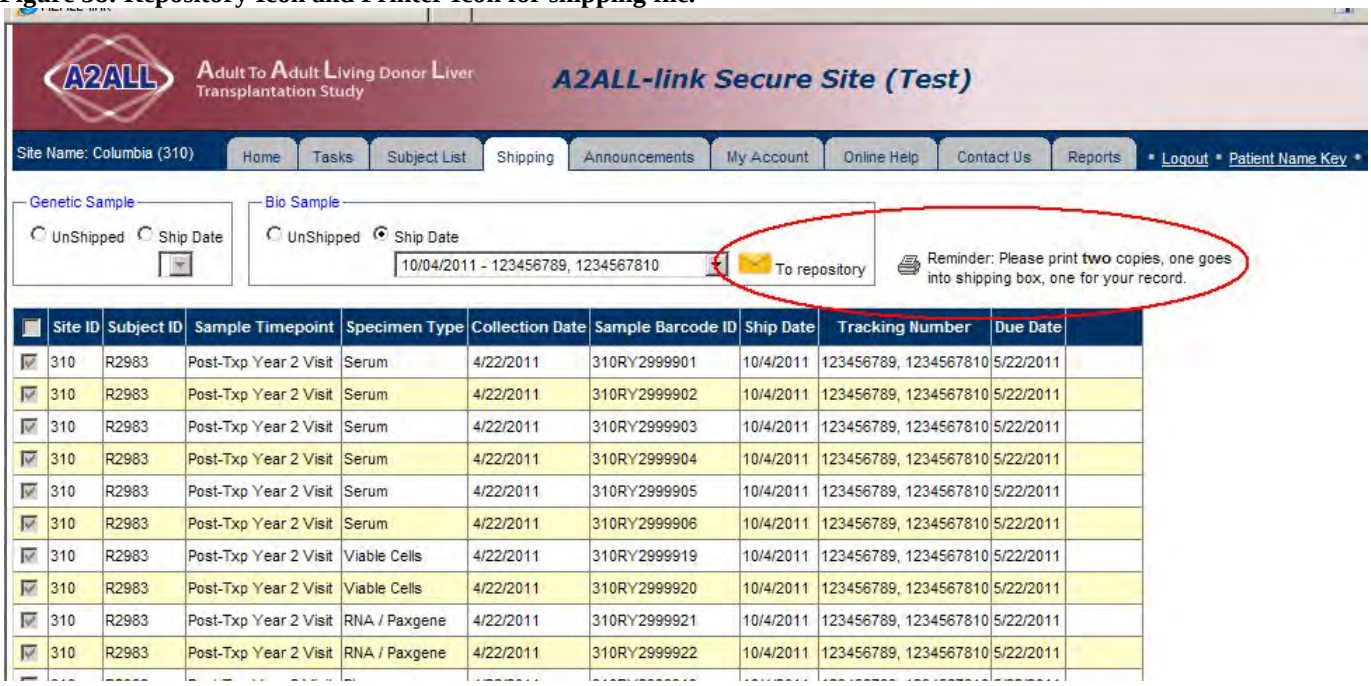
4. Click the “Shipping Information” button.
5. A dialog box will appear (Figure 37 below).
6. Enter the ship date.
7. Choose a carrier from the drop down list.
8. Enter the tracking number. If there is more than one box going out, enter multiple tracking numbers separated by a comma.
9. Note that the system tells you how many PaxGene samples you have. One tray holds 49 PaxGene tubes. It will also tell you how many aliquot samples you have. One tray holds 81 aliquots. It will tell you how many trays and how many empty slots you have. Make sure you review and reconcile these samples prior to shipping.
10. Click “Confirm” after entering and reconciling the sample and shipping information.

Figure 37: Shipping Information Dialog Box



11. The dialog box will close and the "Repository and Print" icon will be available, see Figure 38 below.

Figure 38: Repository Icon and Printer Icon for shipping file.

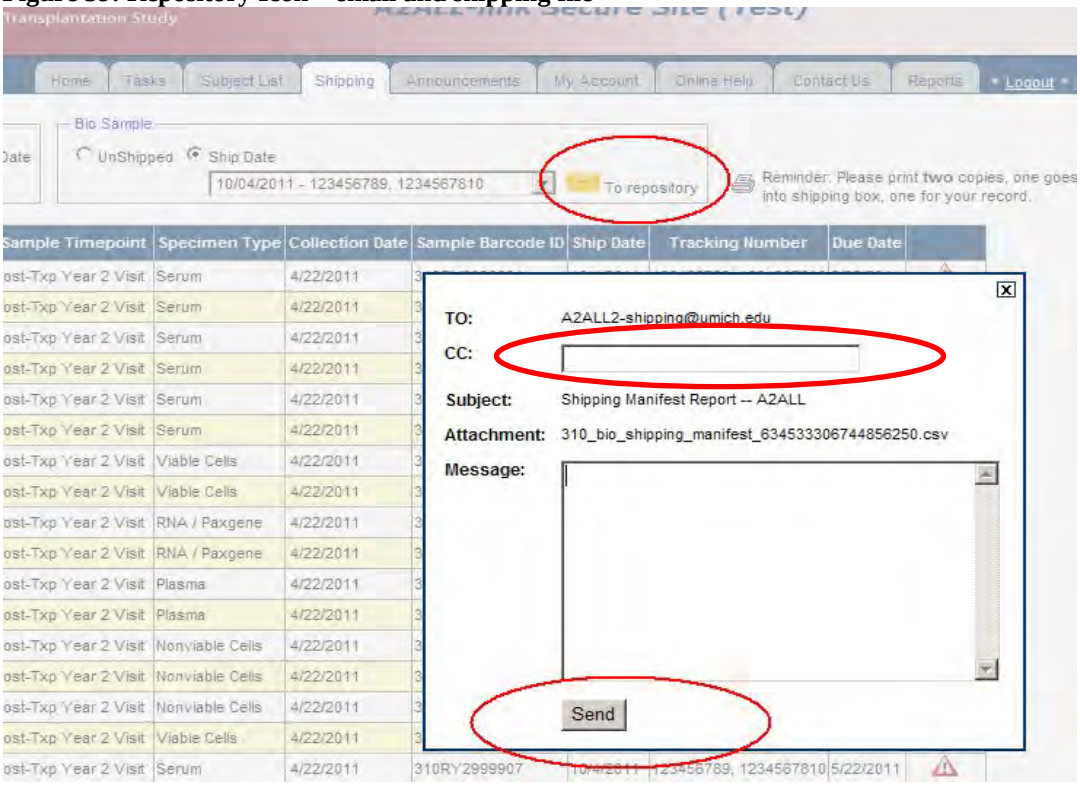


Site ID	Subject ID	Sample Timepoint	Specimen Type	Collection Date	Sample Barcode ID	Ship Date	Tracking Number	Due Date
310	R2983	Post-Txp Year 2 Visit	Serum	4/22/2011	310RY2999901	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	Serum	4/22/2011	310RY2999902	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	Serum	4/22/2011	310RY2999903	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	Serum	4/22/2011	310RY2999904	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	Serum	4/22/2011	310RY2999905	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	Serum	4/22/2011	310RY2999906	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	Viable Cells	4/22/2011	310RY2999919	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	Viable Cells	4/22/2011	310RY2999920	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	RNA / Paxgene	4/22/2011	310RY2999921	10/4/2011	123456789, 1234567810	5/22/2011
310	R2983	Post-Txp Year 2 Visit	RNA / Paxgene	4/22/2011	310RY2999922	10/4/2011	123456789, 1234567810	5/22/2011

12. Click the "Printer" icon to print the manifest. Print at least two copies, one for the shipping box, and one as a source document. If you are shipping more than one box on the same manifest, print the appropriate number of extra manifests to be included in each box in your shipment .

13. Click the "Repository" icon (yellow envelope).

Figure 39: Repository Icon – email and shipping file



This will automatically send an email, and a shipping manifest to the repository and the DCC. It is very important to complete this task on the day of shipment. The email address: A2ALL2-shipping@umich.edu includes both the repository, and the DCC email addresses (monitors are included in this email). Please include an email address for your site in the "CC": column. This will ensure, that you are included in the shipment confirmation email from the repository. Feel free to include any message you may have regarding the shipment. Make sure to Click the "**SEND**" button on the bottom on the shipping page. This will alert the repository that a shipment is on its way.

14. To review or print previous manifests, click the "Ship Date" button, and scroll down through the drop-down menu of previous shipments. **Do not attempt to edit previous shipping manifests**. If a manifest needs to be revised, please contact the DCC.

7.6. Genetic Sample Shipping

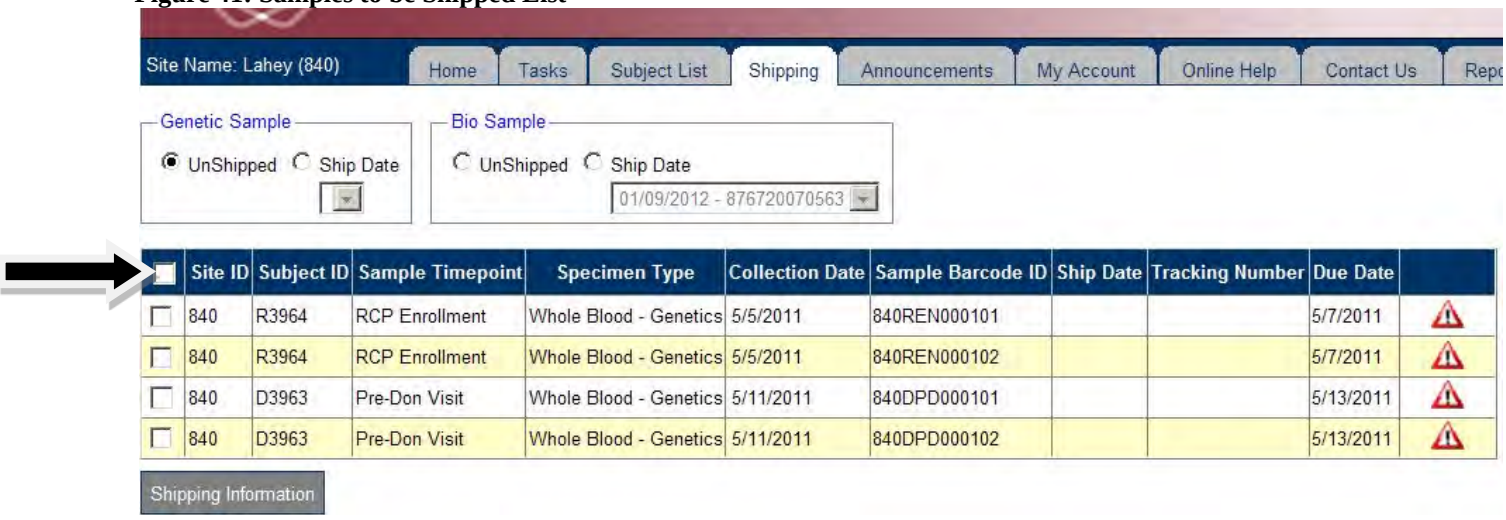
You must ship all Genetic Samples to Fisher BioServices (Rockville, MD address in MOO) within 48 hrs. Please refer to the MOO for sample handling and packaging information.

1. Click the "Shipping" tab.
2. On the Genetic side of the page, click "Unshipped".

Figure 40: Shipping Tab View

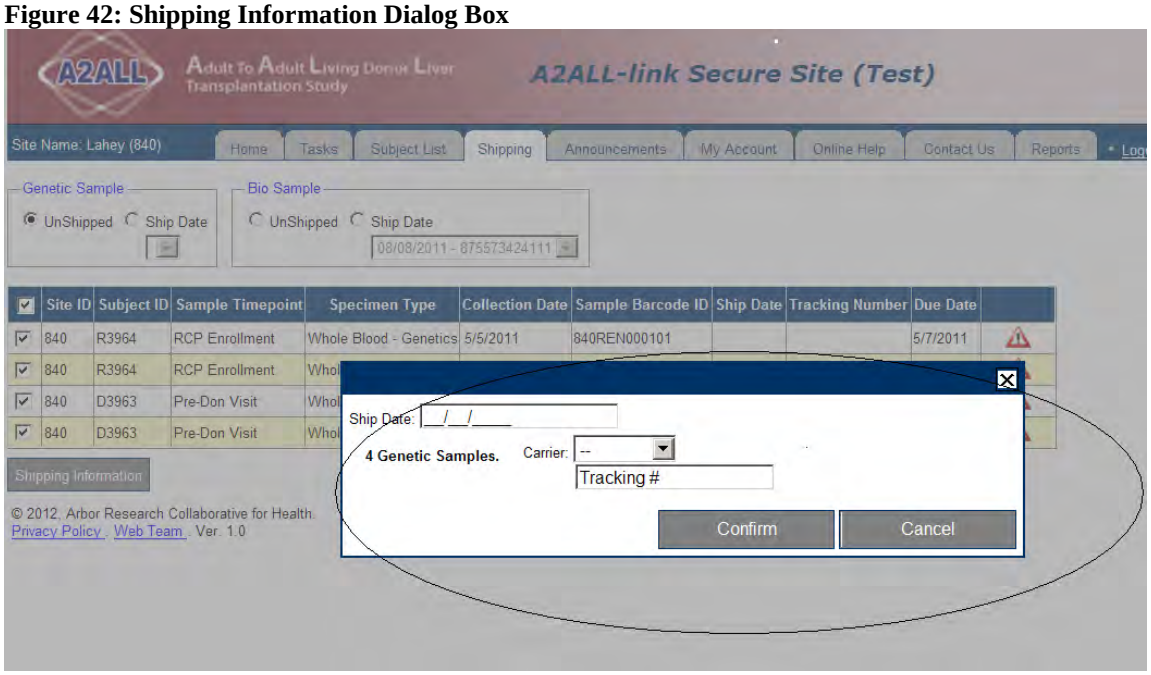
3. A list of all unshipped samples will be generated. For almost every instance, you should select "All" by clicking the box on the header row in the first column. This will check all of the samples on the list.

Figure 41: Samples to be Shipped List



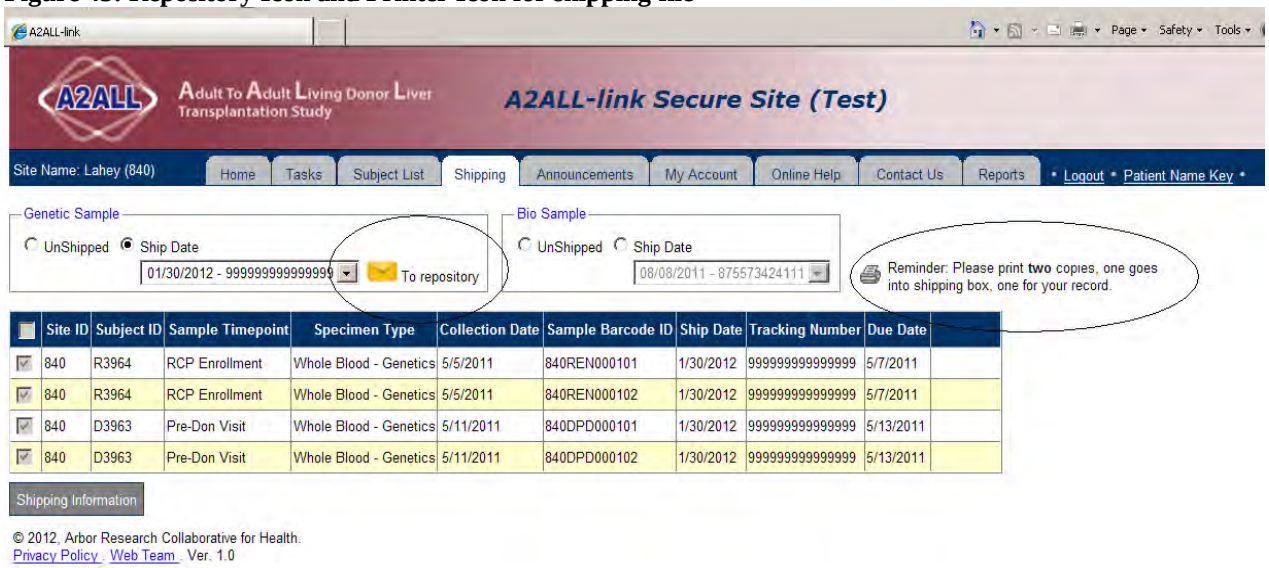
4. Click the "Shipping Information" button.
5. A dialog box will appear.
6. Enter the ship date.
7. Choose a carrier from the drop down list.
8. Enter the tracking number. If there is more than one box going out, enter multiple tracking numbers separated by a comma.
9. Note that the system tells you how many Genetic samples you have. Each shipping container will hold 8 samples (4 subjects with 2 samples each). Make sure you review and reconcile these samples prior to shipping.
10. Click "Confirm" after entering and reconciling the sample and shipping information.

Figure 42: Shipping Information Dialog Box



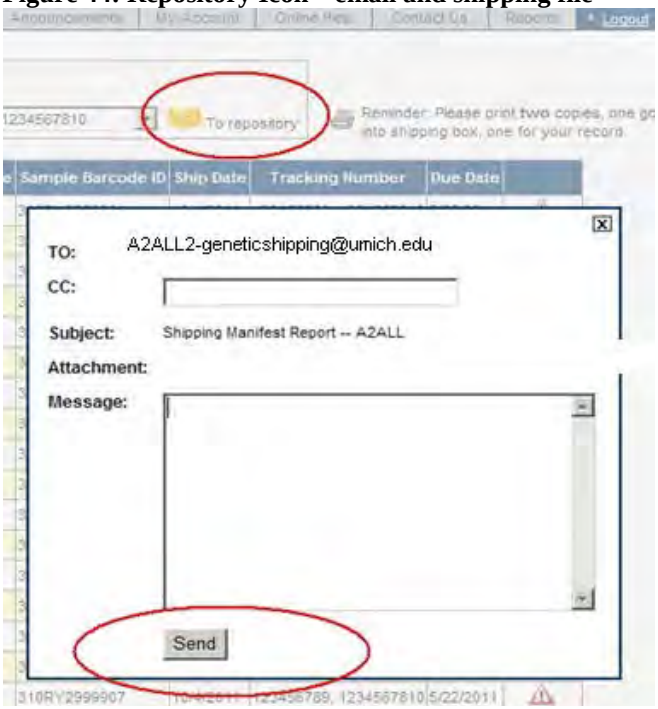
11. The dialog box will close and the “Repository and Print” icon will be available, see Figure 43 below

Figure 43: Repository Icon and Printer Icon for shipping file



12. Click the “Printer” icon to print the manifest. Print at least two copies, one for the shipping box and one as a source document. If you are shipping more than one box on the same manifest, print one for each shipping container.
13. Click the “Repository” icon (yellow envelope).

Figure 44: Repository Icon – email and shipping file



This will automatically send an email, and a shipping manifest to the repository and the DCC. It is very important to complete this task on the day of shipment. The email address: A2ALL2-

geneticshipping@umich.edu includes both the repository and the DCC email addresses (monitors are included in this email). Include your email address under "CC": to be included in the shipment confirmation email. Feel free to include any message you may have regarding the shipment. Make sure to Click the **SEND** button on the bottom on the shipping page. This will alert the repository that a shipment is on its way.

14. To review or print previous manifests, click the "Ship Date" button, and scroll down through the drop-down menu of previous shipments. Do not make any edits on previous shipments. If revisions to previously sent manifests are needed, please contact the DCC.

7.7. HCV Microscope Slides Shipping

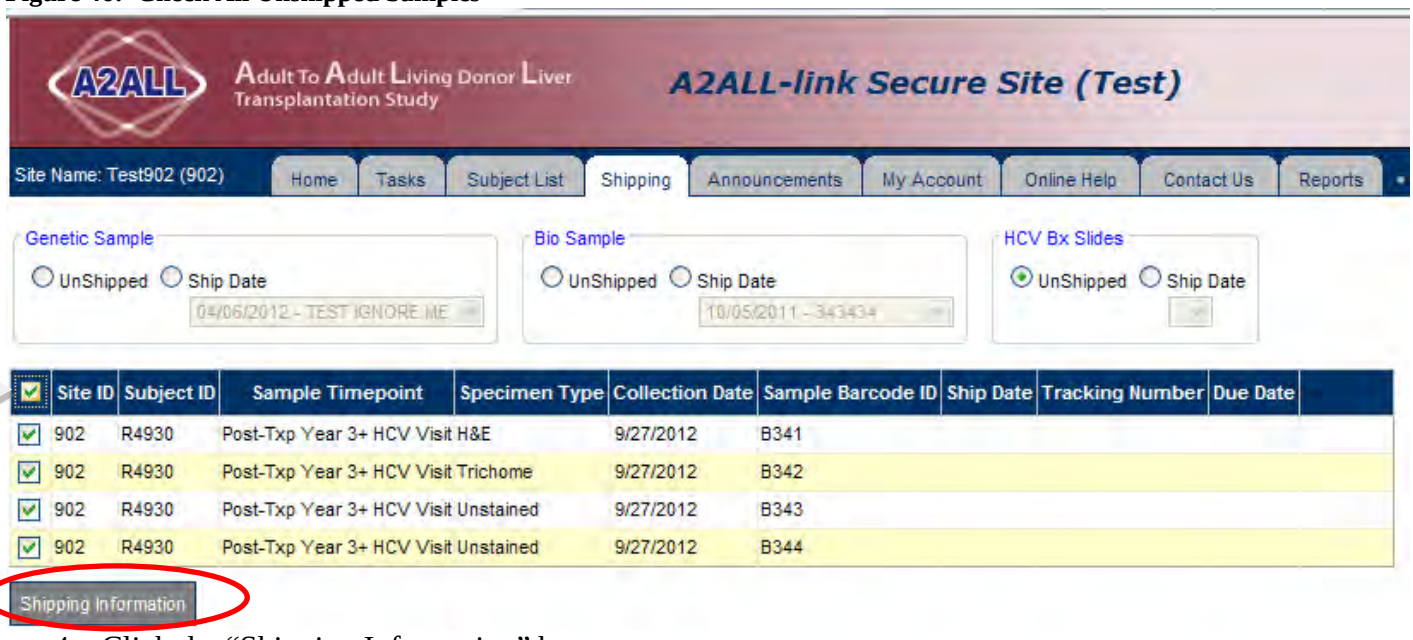
The microscope slides are shipped quarterly unless otherwise specified (began December 2012), during the first week of the month to Toronto where the pathologist (Dr. Adeyi) will perform a central reading.

1. Click the "Shipping" tab.
2. On the HCV of the page, click "Unshipped".

Figure 45: HCV Shipping Selection

3. A list of all unshipped samples will be generated. For almost every instance, you should select "All" by clicking the box on the header row in the first column. This will check all of the samples on the list.

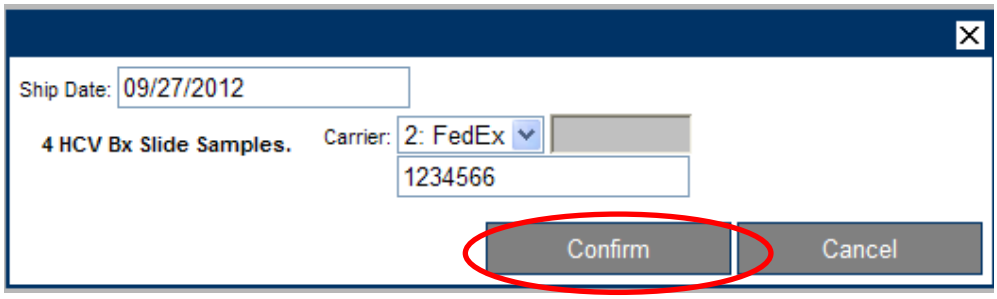
Figure 46: Check All Unshipped Samples



4. Click the "Shipping Information" button.
5. A dialog box will appear.

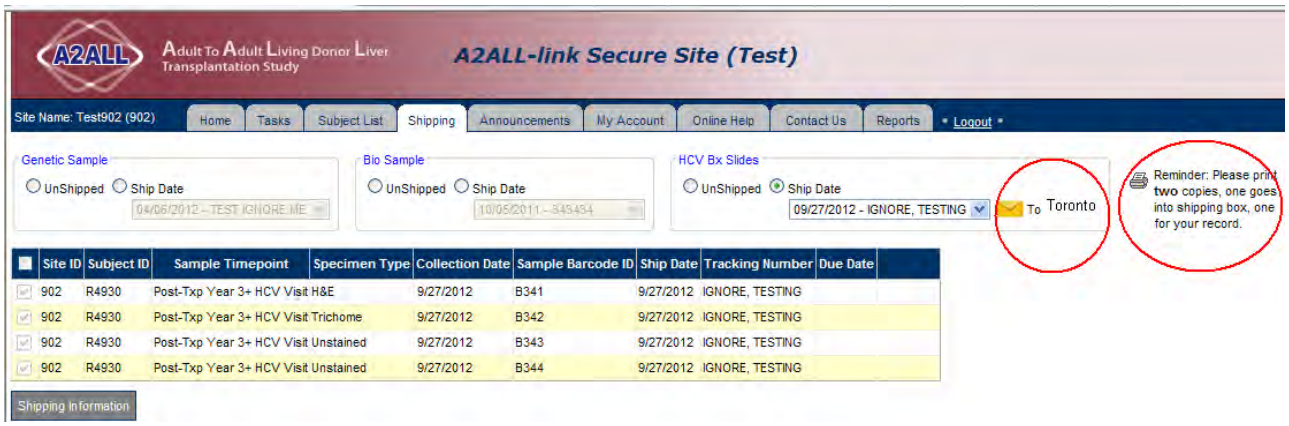
6. Enter the ship date.
7. Choose a carrier from the drop down list.
8. Enter the tracking number. If there is more than one box going out, enter multiple tracking numbers separated by a comma.
9. Note that the system tells you how many samples you have.
10. Click "Confirm" after entering and reconciling the sample and shipping information

Figure 47: HCV Bx Slides Shipping Info Dialog Box



11. The dialog box will close, and the "Repository and Print" icon will be available, see Figure 47 below.

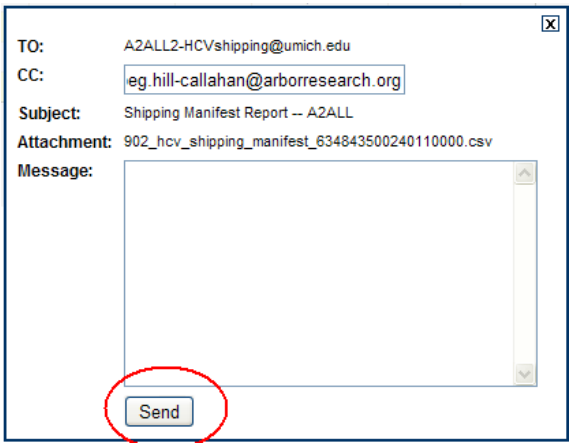
Figure 48: Print Manifest



12. Click the "Printer" icon to print the manifest. Print at least two copies, one for the shipping box and one as a source document. If you are shipping more than one box on the same manifest, print one for each shipping container.
13. Click the "Email" icon (yellow envelope).
14. A dialog box will appear.

This will automatically send an email and a shipping manifest to Toronto, and the DCC. It is very important to complete this task on the day of shipment. The email address: A2ALL2-HCVshipping@umich.edu includes both the pathologist (Dr. Adeyi) at Toronto, and the DCC email addresses (monitors are included in this email). Include your email address under "CC": to be included in the shipment confirmation email. Feel free to include any message you may have regarding the shipment. Make sure to Click the "SEND" button on the bottom on the shipping page. This will alert Dr. Adeyi's office (Toronto) that a shipment of HCV slides is on its way.

Figure 49: Shipping Email Confirmation



15. To review or print previous manifests, click the "Ship Date" button, and scroll down through the drop-down menu of previous shipments. Do not make any edits on previous shipments. If revisions to previously sent manifests are needed, please contact the DCC.

8. Case Report Forms (eCRFs)

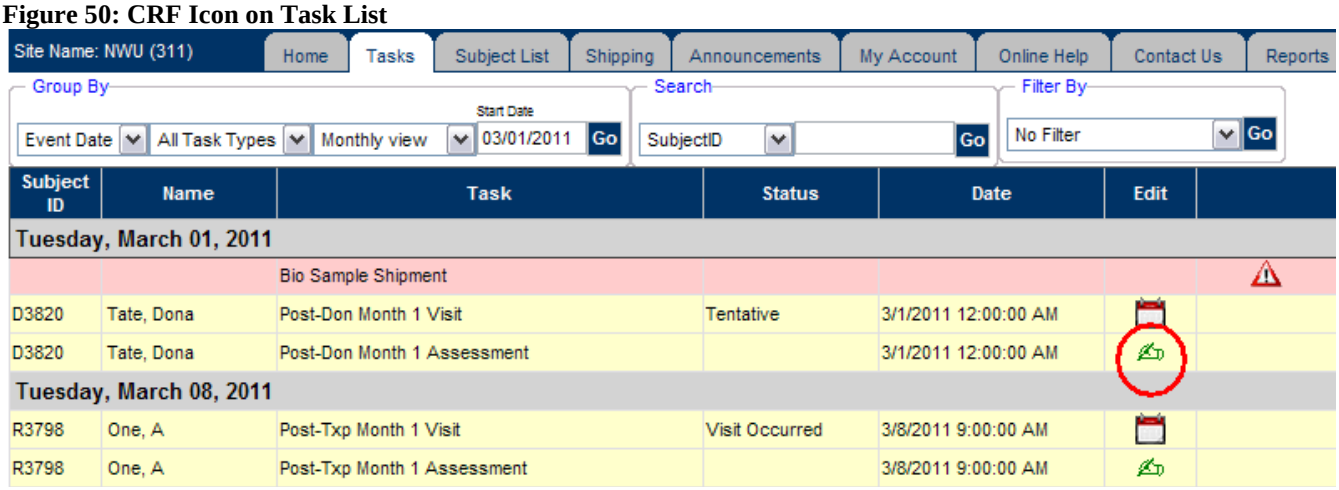
8.1. Overview

There are two general types of eCRFs in the study; those that are associated with a visit, and those that are event-driven.

You will find links to the visit eCRFs on the "Tasks "list. To open the link to fill out an eCRF, click the icon that shows a hand holding a pencil on the "Tasks" list.

Event-driven eCRFs (hospitalization, complication, etc) can be accessed by clicking the "CRF" link next to the subject's ID on the "Subject List."

Figure 50: CRF Icon on Task List



8.2. Data Entry

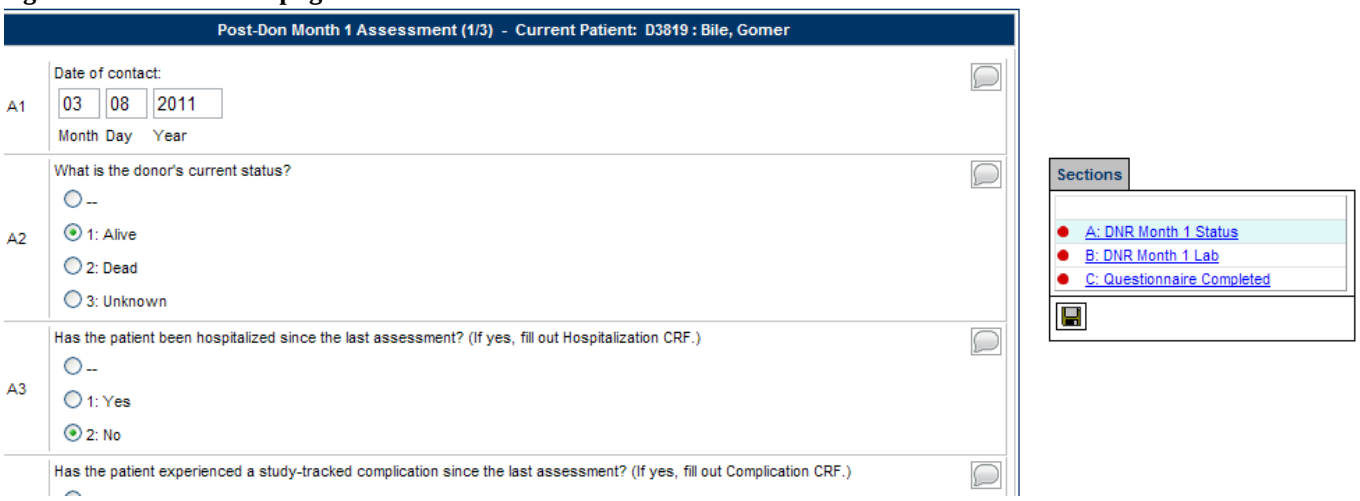
eCRFs are divided into Sections (i.e. status, labs, imaging, etc.). Each section has a "stop-light" icon. Red means no data has been entered. Yellow means that some data has been entered, but the form is not complete. Green means that the section has all data fields completed.

The final section of each CRF is a single question that asks you if you are done entering data on the form. If you answer "yes" then the stop light for that section turns green. If you answer "no", it stays yellow, letting you (and the DCC) know that you still have data to enter
You have 3 weeks from the time a scheduled visit has occurred to complete the eCRF associated with that visit. If you do not complete the CRF in that timeframe, you will get an overdue warning.

Use the "Tab" key to navigate through fields. Date fields will automatically tab you through the day, month and year fields.

Each section has its own "Save" button.
Each eCRF has a "questionnaire complete" question. If all data has been entered, click "yes" for questionnaire complete, the stoplight will turn green. If there are outstanding data, do not click "yes" the stoplight will remain red.

Figure 51: CRF with Stoplights

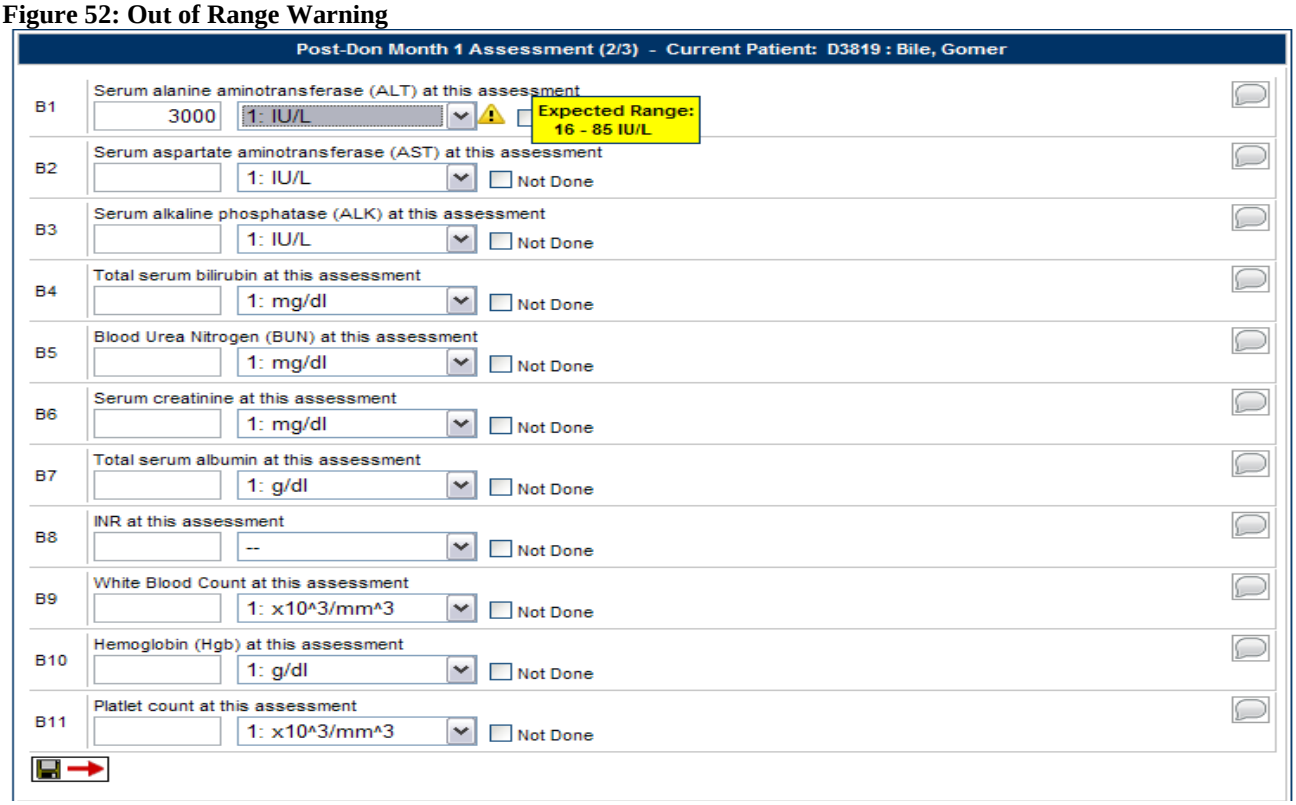


8.2.1. Ranges

All lab data fields have ranges coded to entered values. If you enter a value that's out of range, you will get a warning when you tab out of the field telling you that the value you entered is out of range, and what the expected range is. You can either choose to continue without changing the value, or if the value is correct, you can continue without changing the value. For more information about lab ranges (United States only), please refer to the MOO.

If you do not change the out of range value, you will receive another warning when you try to save the page. At that point, you will again be given the option to either fix the values or continue your save. Continuing to ignore the warnings without fixing or confirming the out of range values will result in queries.

Figure 52: Out of Range Warning

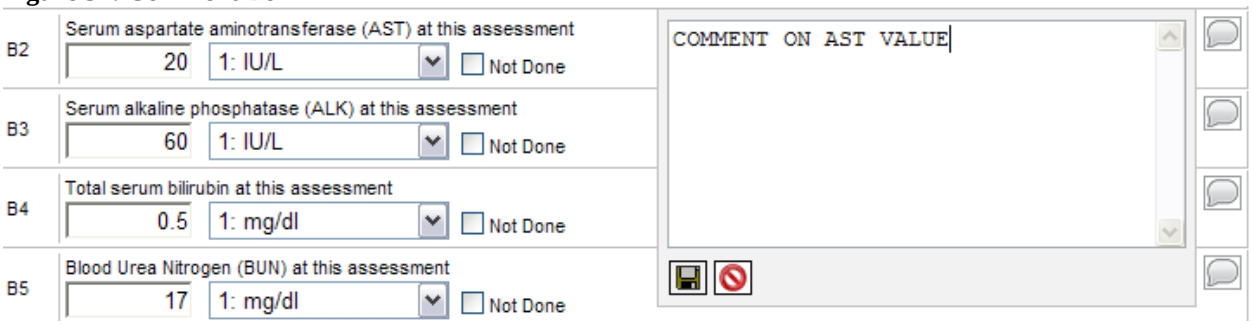


8.2.2. Comments

All fields on eCRFs have Comment fields. Click the "Comment" icon. Enter your comment and click the save button. Fields with comments have an icon that indicates text was entered. Please add a comment to all out of range lab values. This will prevent future queries.

Figure 53: Comment Icons

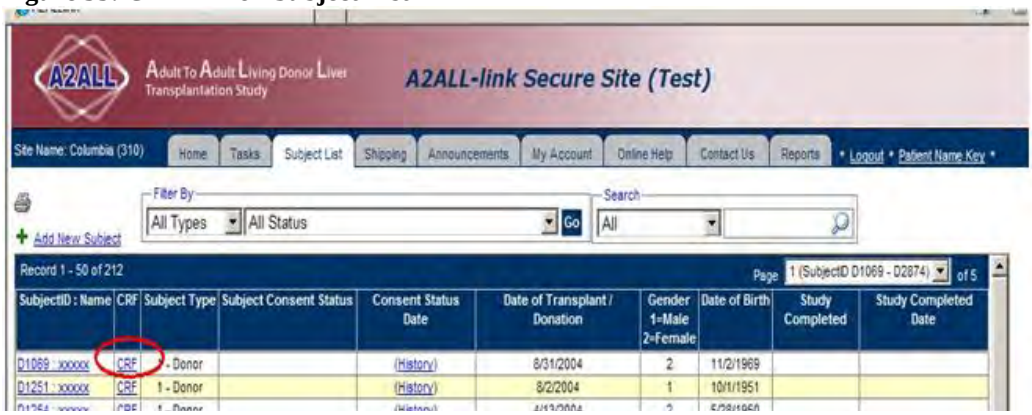
Figure 54: Comment Box



8.3. Event Driven eCRFs

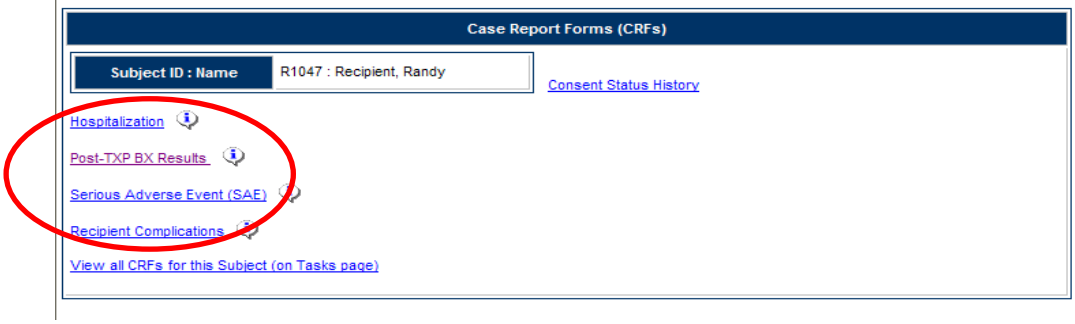
1. Click the "CRF" link on the "Subject List."

Figure 55: CRF link on Subject List



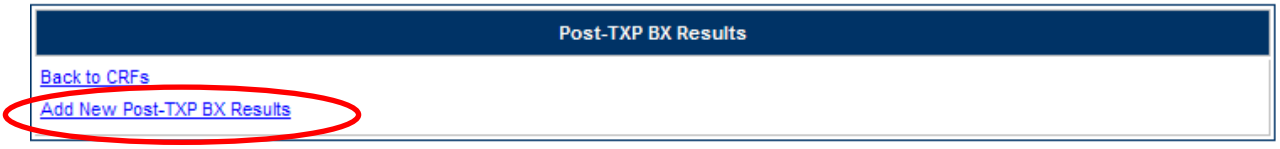
2. Click the type of form you want to fill out.

Figure 56: CRF types "xxx" eCRF



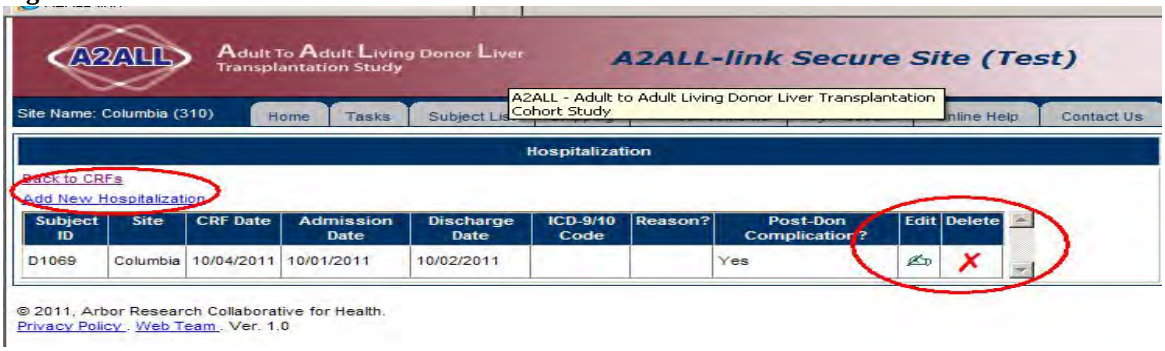
3. Click "add a new xxx".

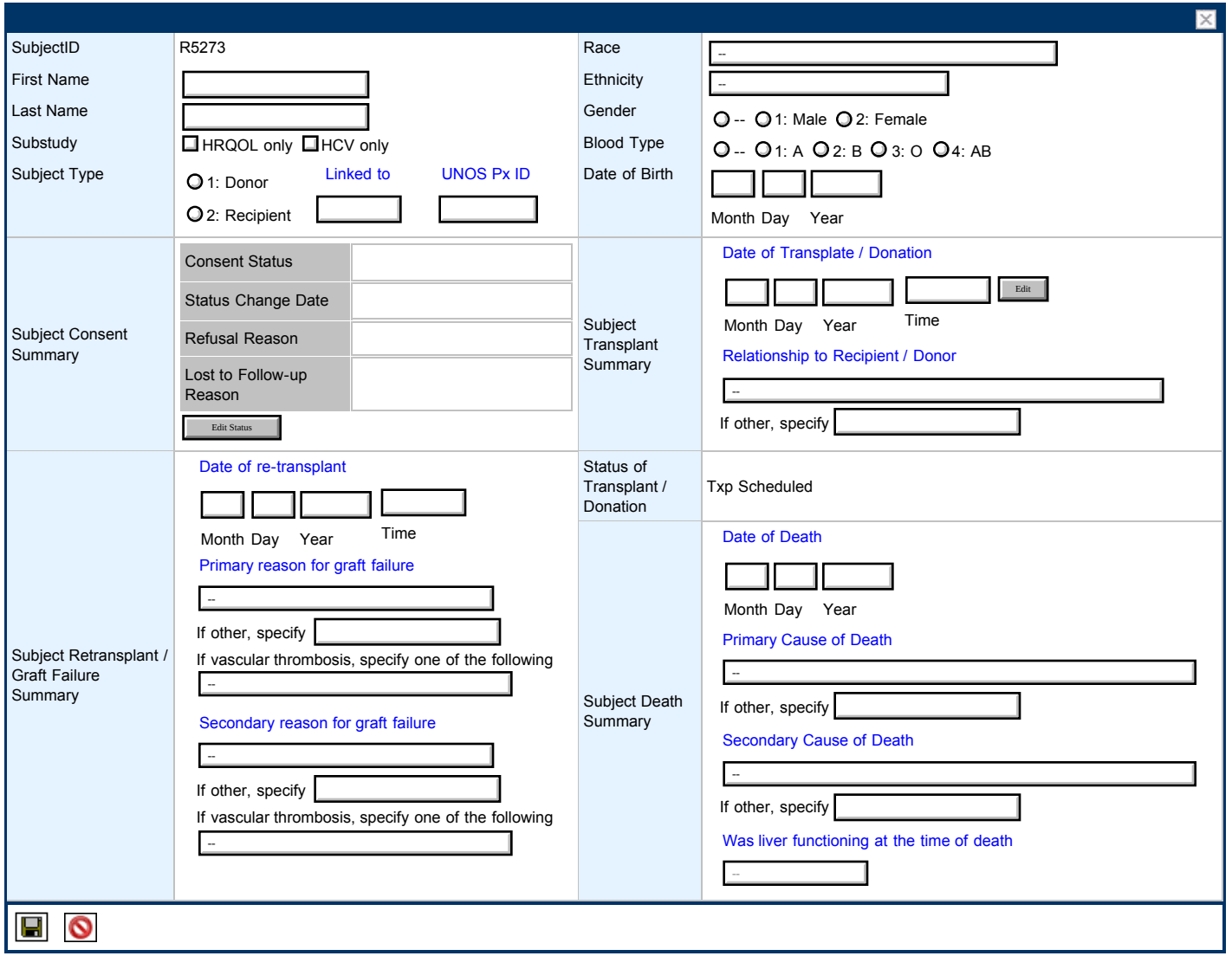
Figure 57: Event Driven eCRFs



4. Enter the data.
5. Save the form.
6. The form appears on the CRF-specific table. You can edit, delete or add a new form from this menu.

Figure 58: Event Driven CRF table





SubjectID	R5273	Race	--
First Name		Ethnicity	--
Last Name		Gender	-- 1: Male 2: Female
Substudy	HRQOL only HCV only	Blood Type	-- 1: A 2: B 3: O 4: AB
Subject Type	1: Donor Linked to UNOS Px ID 2: Recipient	Date of Birth	Month Day Year
Subject Consent Summary	Consent Status Status Change Date Refusal Reason Lost to Follow-up Reason Edit Status	Subject Transplant Summary	Date of Transplate / Donation Edit Month Day Year Time Relationship to Recipient / Donor -- If other, specify
Subject Retransplant / Graft Failure Summary	Date of re-transplant Month Day Year Time Primary reason for graft failure -- If other, specify If vascular thrombosis, specify one of the following -- Secondary reason for graft failure -- If other, specify If vascular thrombosis, specify one of the following --	Status of Transplant / Donation	Txp Scheduled
		Subject Death Summary	Date of Death Month Day Year Primary Cause of Death -- If other, specify Secondary Cause of Death -- If other, specify Was liver functioning at the time of death --

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

DNR Intraop

Site ID:	902
Subject ID : Name	D3901 : TF5ZP3OE, RNCENIy5

All source documents should contain all of the information entered on this eCRF. The PI is responsible for answering the anatomy and reconstruction questions and signing off on the intraoperative worksheet within 24 hours after surgery.

A1 Date of donation surgery: [ ] [ ] [ ] Month Day Year

Please complete a hospitalization CRF for the donation admission.

B1 Donor height closest to the time of donation: [ ] Inches

The answers to B1 and B2 are linked to C1 and C2 on the RCP IntraOp eCRF if they don't match a warning will show.

B2 Donor weight closest to the time of donation: [ ] Kilograms

B3 Serum alanine aminotransferase (ALT) closest to the time of donation [ ] IU/L ☐Not Done

B4 Serum aspartate aminotransferase (AST) closest to the time of donation [ ] IU/L ☐Not Done

B5 Serum alkaline phosphatase (ALK) closest to the time of donation [ ] IU/L ☐Not Done

B6 Total bilirubin closest to the time of donation [ ] mg/dl ☐Not Done

B7 Serum creatinine closest to the time of donation [ ] mg/dl ☐Not Done

B8 Albumin closest to the time of donation [ ] g/dl ☐Not Done

B9 Blood urea nitrogen (BUN) closest to the time of donation [ ] mg/dl ☐Not Done

B10 INR closest to the time of donation [ ] INR Units ☐Not Done

B11 White blood cell (WBC) count closest to the time of donation [ ] x10^3/mm^3 ☐Not Done

B12 Hemoglobin (Hgb) closest to the time of donation [ ] g/dl ☐Not Done

B13 Platelet count closest to the time of donation [ ] x10^3/mm^3 ☐Not Done

B14 Right Lobe Liver volume (CT or MR): [ ] cc

B15 Left Lobe Liver volume (CT or MR):

cc

B16 Spleen Volume (CT or MR):
cc

C1 Was the donation procedure aborted before completion? (if no, go to question C-5)
If yes, answer C2, C3 and C4.
-- / 1: Yes / 2: No

If yes to procedure abortion, why was the procedure aborted? (Check all that apply)
Click to Expand/Collapse
- Quality of donor liver
- Insufficient liver mass
- Technical difficulties in the donor
- Donor instability
- Unexpected medical findings in the recipient
- Recipient instability
- Recipient death on table
- Other

Specify other reason for procedure abortion:

C2 Did the donor receive general anesthesia?
If no, skip to F1.
-- / 1: Yes / 2: No

C3 Was the liver parenchyma divided?
-- / 1: Yes / 2: No

C4 Was the lobe removed from the donor?
If no, answer C5 then skip to and answer C8 as well as C12, C13, C14, C15 and C16.
-- / 1: Yes / 2: No

C5 Was the donation procedure performed laparoscopically?
If a portion of the donation surgery utilized hybrid procedure answer as a laparoscopic procedure.
-- / 1: Yes / 2: No

C6 Was the donated lobe transplanted?
-- / 1: Yes / 2: No

C7 Was the donated graft transplanted into the originally-intended recipient? (if yes, go to question C-8)
-- / 1: Yes / 2: No

If no to graft transplantation, why wasn't the resected graft transplanted into the recipient? (Check all that apply)
Click to Expand/Collapse
- Quality of donor liver
- Insufficient liver mass
- Recipient instability
- Unexpected medical findings in the recipient
- Recipient death on table
- Other

Specify other reason why the resected graft was not transplanted into the recipient:

C8 Was a pre-operative or intraoperative biopsy of the donor liver performed? (if no, go to question C-9)
-- / 1: Yes / 2: No

This refers to a biopsy performed other than the biopsy performed to collect the required study liver tissue samples. If a biopsy was not performed, answer no.

If yes to pre-op/intraop liver biopsy:

Do not answer these questions if a biopsy was not performed.

What was the percentage of macrovesiclar fat noted on the biopsy report?
1: %

What was the percentage of microvesiclar fat noted on the biopsy report?
1: %

Were other findings noted?
-- / 1: Yes / 2: No

This is answered if C8 is yes.

Other findings (specify):

C9 Lobe recovered:
--

The answer to this question is linked to the RCP IntraOp question C4, if it doesn't match a warning will show.

C10 Was the middle hepatic vein included?
--

The answer to this question is linked to the RCP IntraOp question D6, if it doesn't match a warning will show.

C11 What was the weight of the resected lobe (graft weight)?
gm

The answer to this question is linked to the RCP IntraOp question C5, if it doesn't match a warning will show.

C12 Was auto-transfusion used?
-- / 1: Yes / 2: No

Anesthesia records need to be available for this data element.

If yes to auto-transfusion, total amount transfused:
cc

Do not use decimal points, the system only allows whole numbers.

C13 Was banked blood given to the subject during the donation surgery?
-- / 1: Yes / 2: No

Anesthesia records need to be available for this data element.

Number of predonated autologous units:

Autologus is defined as being from the subject.

Number of non-autologous units:

Non-autologus is defined as not from the subject.

C14 Did the subject experience any episode(s) of systolic BP<100 mmHg during the surgery? (if no, go to question C-16)
-- / 1: Yes / 2: No

Anesthesia records need to be available for this data element. Each episode counts as 5 minutes.

If yes, indicate total duration of the episode(s). Add together if more than one episode.
min

C15 Did the subject experience systolic BP<80 mmHg for 5 or more minutes during the surgery?
-- / 1: Yes

Anesthesia records need to be available for this data element.

2: No

C16

Did any intraoperative injuries occur? (if no, go to question C-17)

--
1: Yes
2: No

If yes, which structure(s) were injured? (check all that apply)

Click to Expand/Collapse

- Bile duct
- Hepatic artery
- Portal vein
- Other

Specify other structure injured:

C17

Cross clamp time (24-hour clock time):

The answer to this question us linked to the RCP IntraOp question C6, if it doesn't match a warning will show.

D1

Select the figure below that indicates the donor's biliary anatomy:

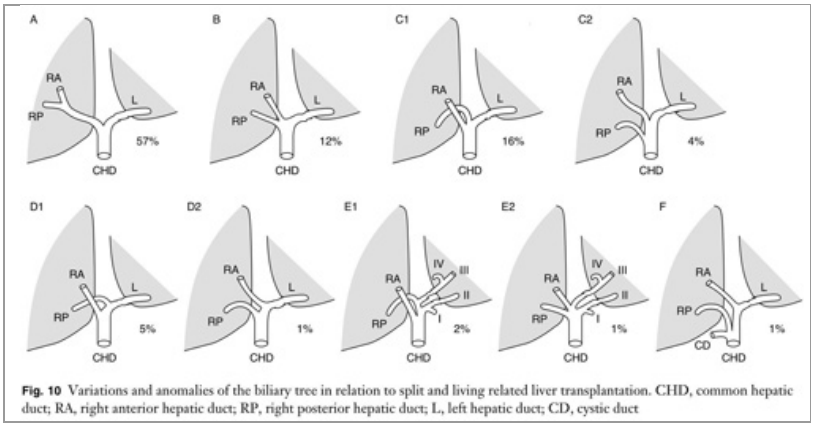


Fig. 10 Variations and anomalies of the biliary tree in relation to split and living related liver transplantation. CHD, common hepatic duct; RA, right anterior hepatic duct; RP, right posterior hepatic duct; L, left hepatic duct; CD, cystic duct

If the donor's biliary anatomy does not match any of the drawings, choose the one it closely resembles and enter a comment in the comment text box.

--

D2

Select the figure below that indicates the donor's hepatic venous anatomy:

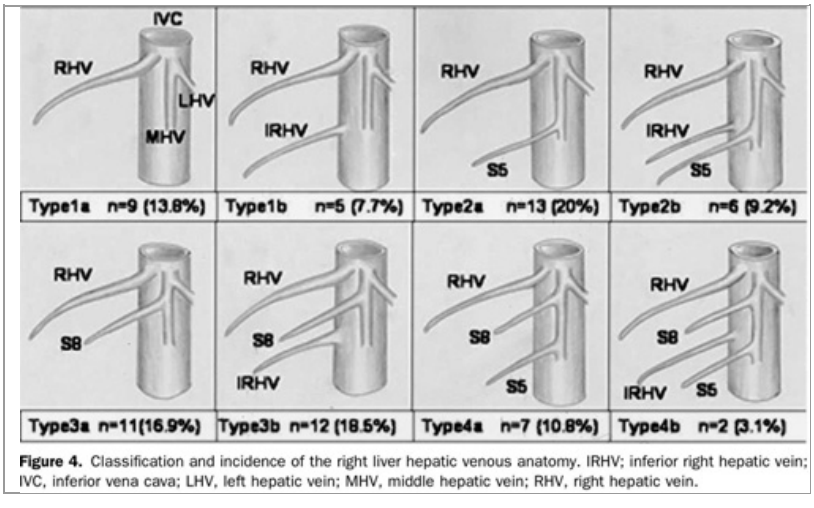


Figure 4. Classification and incidence of the right liver hepatic venous anatomy. IRHV; inferior right hepatic vein; IVC, inferior vena cava; LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein.

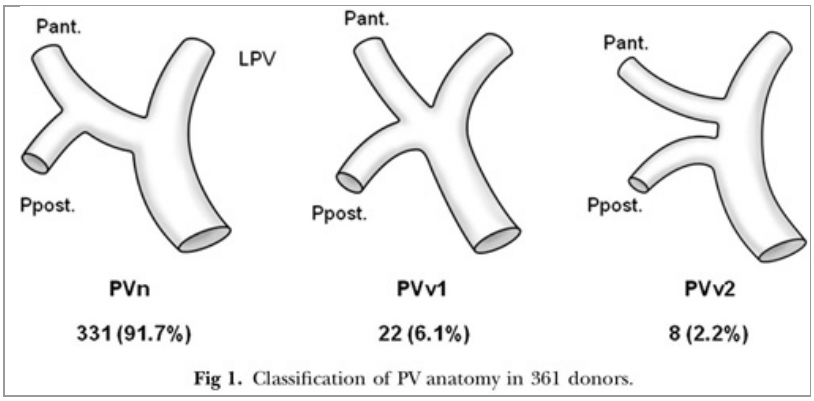
If the donor's hepatic anatomy does not match any of the drawings, choose the one it closely resembles and enter a comment in the comment text box.

--

D3

Right lobe graft hepatic venous anatomy: Select vein >5mm preserved for anastomosis:

--
1: Right hepatic vein including all segments
2: Right hepatic vein with separate segment 8
3: Right hepatic vein with segment 5 and 8 separate

	○ 4: Right hepatic vein with segment 6 separate ○ 5: Other	
	Specify Other:	
D4	Left lobe graft hepatic venous anatomy: ⊙ -- ○ 1: Single orifice for segments 2, 3, 4 ○ 2: Single orifice for segments 2 and 3 with separate orifice for segment 4 ○ 3: Single orifice for segments 3 and 4 with separate orifice for segment 2 ○ 4: Other	
	Specify Other:	
D5	Left lateral segment graft hepatic venous anatomy: ⊙ -- ○ 1: Single orifice for segments 2 and 3 ○ 2: Separate orifices for segment 2 and segment 3 ○ 3: Other	
	Specify Other:	
D6	Select the figure below that indicates the donor's portal venous anatomy:  **Fig 1.** Classification of PV anatomy in 361 donors. ⊙ -- ○ 1: PVn ○ 2: PVv1 ○ 3: PVv2 ○ 4: Other	
D7	Select the figure below that indicates the donor's hepatic arterial anatomy:	

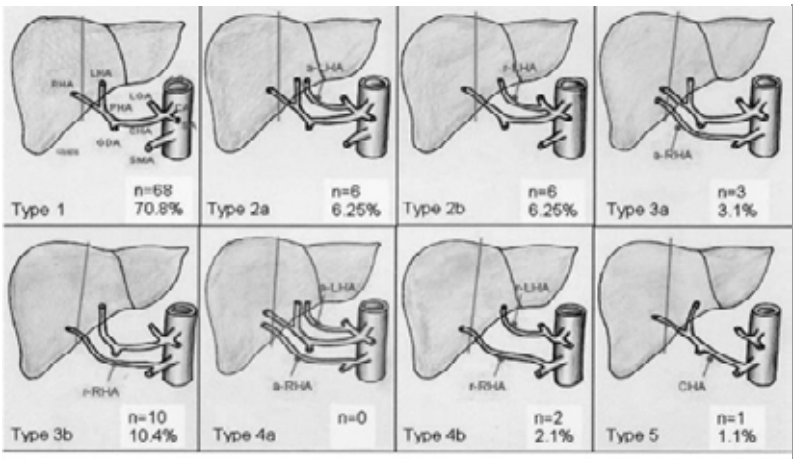


Figure 2. Classification and incidence of the hepatic artery anatomy. AO, aorta; CA, celiac axis; CHA, common hepatic artery; GDA, gastroduodenal artery; LGA, left gastric artery; LHA, left hepatic artery; PHA, proper hepatic artery; RHA, right hepatic artery; SA, splenic artery; SMA, superior mesenteric artery.

--

D8 Does the arterial supply to segment 4 arise from the left hepatic artery or the right hepatic artery:

- (•) --
- ( ) 1: Left hepatic artery
- ( ) 2: Right hepatic artery

E1 Questionnaire Completed

Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.

This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC):

- (•) --
- ( ) 1: Yes
- ( ) 2: No

eCRF revised 10252012
Annotation revised 07232013

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Post-Don Week 1 Assessment

Site ID:	902

Subject ID : Name	D3901 : TF5ZP3OE, RNCENIy5

A1 Date of contact: [ ] [ ] [ ] Month Day Year

Week 1 visit window is Donation Date - Day 18

A2 What is the donor's current status? (if dead, skip to section C of this assessment then enter death information on subject page)

- ⊙ --
- ○ 1: Alive
- ○ 2: Dead
- ○ 998: Unknown

Enter the date of death and cause of death if known in the subject dialog box. Update the consent status also, this can be done through the subject dialog box as well.

A3 Has the patient been hospitalized since the last assessment? (If yes, fill out Hospitalization CRF.)

- ⊙ --
- ○ 1: Yes
- ○ 2: No

Check yes, if the subject was re-hospitalized after their donation hospitalization.
Remember to complete the Hospitalization CRF for the donation admission.

A4 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)

- ⊙ --
- ○ 1: Yes
- ○ 2: No

A5 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)

- ⊙ --
- ○ 1: Yes
- ○ 2: No

A6 Donor medical condition at this assessment.

- ⊙ --
- ○ 1: Patient in ICU
- ○ 2: Hospitalized, not in ICU
- ○ 3: In rehab facility
- ○ 4: Not hospitalized

A7 Donor on ventilator at this assessment?

- ⊙ --
- ○ 1: Yes
- ○ 2: No
- ○ 998: Unknown

B1 Donor weight at this assessment [ ] Pounds

This question was added in June 2012, for subjects who already completed this visit, the sites will be asked to go back and add this data.

B2 Serum alanine aminotransferase (ALT) at this assessment [ ] IU/L ☐ Not Done

Week 1 labs are required by the Core Protocol. These labs can be drawn +/- 2 days from the visit date.

Serum aspartate aminotransferase (AST) at this assessment

B3	IU/L ☐Not Done	
B4	Serum alkaline phosphatase (ALK) at this assessment IU/L ☐Not Done	
B5	Total serum bilirubin at this assessment mg/dl ☐Not Done	
B6	Blood Urea Nitrogen (BUN) at this assessment mg/dl ☐Not Done	
B7	Serum creatinine at this assessment mg/dl ☐Not Done	
B8	Total serum albumin at this assessment g/dl ☐Not Done	
B9	INR at this assessment INR Units ☐Not Done	
B10	White Blood Count at this assessment x10^3/mm^3 ☐Not Done	
B11	Hemoglobin (Hgb) at this assessment g/dl ☐Not Done	
B12	Platelet count at this assessment x10^3/mm^3 ☐Not Done	
C1	Donor pain survey completed? ⊙-- ○1: Yes ○2: No	The Donor pain study was started September 19, 2012. The survey should be administered 48 - 72 hours post-operatively.
	If yes, Date Completed: Month Day Year	
	If yes, Date Transmitted to DCC: Month Day Year	On the 15th of each month, transmit all surveys not previously transmitted to the DCC by attaching them to tone or more emails addressed to a2all-painsurveys@umich.edu
	If no, why? ⊙-- ○1: Sedation Score ≥ 3 at each attempt ○2: Subject refused ○3: Subject medical/emotional issues precluded survey administration ○4: Administrative/staffing issues	
D1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ⊙-- ○1: Yes ○2: No	

Print

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Tasks

Post-Don Month 1 Assessment

Site ID:	902

Subject ID : Name	D3901 : TF5ZP3OE, RNCENIy5

A1 Date of contact: [ ] [ ] [ ] Month Day Year

The visit window for Month 1 visit is Day 19 - Day 60

A2 What is the donor's current status? (if dead, skip to section C of this assessment then enter death information on subject page)

- (•) --
- ( ) 1: Alive
- ( ) 2: Dead
- ( ) 998: Unknown

Enter the date of death and cause of death if known in the subject dialog box. Update the consent status also, this can be done through the subject dialog box as well.

A3 Has the patient been hospitalized since the last assessment? (If yes, fill out Hospitalization CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

A4 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

A5 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

A6 Donor medical condition at this assessment.

- (•) --
- ( ) 1: Patient in ICU
- ( ) 2: Hospitalized, not in ICU
- ( ) 3: In rehab facility
- ( ) 4: Not hospitalized

A7 Donor on ventilator at this assessment?

- (•) --
- ( ) 1: Yes
- ( ) 2: No
- ( ) 998: Unknown

B1 Donor weight at this assessment [ ] Pounds

This question was added in June 2012, for subjects who already completed this visit, the sites will be asked to go back and add this data.

B2 Serum alanine aminotransferase (ALT) at this assessment [ ] IU/L ☐ Not Done

Month 1 labs are required by the Core Protocol. These labs can be drawn +/- 7 days from the visit date.

Serum aspartate aminotransferase (AST) at this assessment

B3	IU/L ☐Not Done	
B4	Serum alkaline phosphatase (ALK) at this assessment IU/L ☐Not Done	
B5	Total serum bilirubin at this assessment mg/dl ☐Not Done	
B6	Blood Urea Nitrogen (BUN) at this assessment mg/dl ☐Not Done	
B7	Serum creatinine at this assessment mg/dl ☐Not Done	
B8	Total serum albumin at this assessment g/dl ☐Not Done	
B9	INR at this assessment INR Units ☐Not Done	
B10	White Blood Count at this assessment x10^3/mm^3 ☐Not Done	
B11	Hemoglobin (Hgb) at this assessment g/dl ☐Not Done	
B12	Platelet count at this assessment x10^3/mm^3 ☐Not Done	
C1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ◉ -- ○ 1: Yes ○ 2: No	

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Post-Don Month 3 Assessment

Site ID:	902

Subject ID : Name	D3901 : TF5ZP3OE, RNCENIy5

A1 Date of contact: [ ] [ ] [ ] Month Day Year

The Month 3 visit window is Day 61-Day228

A2 What is the donor's current status? (if dead, skip to section D of this assessment then enter death information on subject page)

- (•) --
- ( ) 1: Alive
- ( ) 2: Dead
- ( ) 998: Unknown

Enter the date of death and cause of death if known in the subject dialog box. Update the consent status also, this can be done through the subject dialog box as well.

A3 Has the patient been hospitalized since the last assessment? (If yes, fill out Hospitalization CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

A4 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

A5 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

B1 Donor weight at this assessment [ ] Pounds

This question was added in June 2012, for subjects who already completed this visit, the sites will be asked to go back and add this data.

B2 Serum alanine aminotransferase (ALT) at this assessment [ ] IU/L ☐ Not Done

The three month labs are required by the Core Protocol. These labs can be drawn +/- 7 days from the date of the visit.

B3 Serum aspartate aminotransferase (AST) at this assessment [ ] IU/L ☐ Not Done

B4 Serum alkaline phosphatase (ALK) at this assessment [ ] IU/L ☐ Not Done

B5 Total serum bilirubin at this assessment [ ] mg/dl ☐ Not Done

B6 Total serum albumin at this assessment [ ] g/dl ☐ Not Done

B7 INR at this assessment [ ] INR Units ☐ Not Done

White Blood Count at this assessment

B8	x10^3/mm^3 Not Done	
B9	Hemoglobin (Hgb) at this assessment g/dl Not Done	
B10	Platelet count at this assessment x10^3/mm^3 Not Done	
C1	Liver volume (CT or MR): cc The MR/CT measurements are required by the Core Protocol.	
C2	Spleen Volume (CT or MR): cc	
D1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): -- 1: Yes 2: No Do not check yes until all data elements are completed. If the scans have not been read at the time of completing this CRF, enter a comment here.	

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Post-Don Year Assessment

Site ID:	902

Subject ID : Name	D3901 : TF5ZP3OE, RNCENIy5

A1 Date of contact: [ ] [ ] [ ] Month Day Year

The visit window for the Year 1 Assessment is Day 229 to 18 months -1 day
The visit window for the Year 2 Assessment is 18 months to 30 months-1 day
The visit window for the Year 3 Assessment is 30 months to 42 months- 1 day (etc..) for additional years

A2 What is the donor's current status? (if dead, skip to section C of this assessment then enter death information on subject page)

- (•) --
- ( ) 1: Alive
- ( ) 2: Dead
- ( ) 998: Unknown

Enter the date of death and cause of death if known in the subject dialog box. Update the consent status also, this can be done through the subject dialog box as well.

A3 Has the patient been hospitalized since the last assessment? (If yes, fill out Hospitalization CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

A4 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

A5 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)

- (•) --
- ( ) 1: Yes
- ( ) 2: No

B1 Donor weight at this assessment [ ] Pounds

This question was added in June 2012, for subjects who already completed this visit, the sites will be asked to go back and add this data.

B2 Serum alanine aminotransferase (ALT) at this assessment [ ] IU/L ☐ Not Done

The annual labs are required by the Core Protocol. These labs can be drawn +/- 1 month from the visit date.

B3 Serum aspartate aminotransferase (AST) at this assessment [ ] IU/L ☐ Not Done

B4 Serum alkaline phosphatase (ALK) at this assessment [ ] IU/L ☐ Not Done

B5 Total serum bilirubin at this assessment [ ] mg/dl ☐ Not Done

B6 Total serum albumin at this assessment [ ] g/dl ☐ Not Done

B7 INR at this assessment [ ] INR Units ☐ Not Done

White Blood Count at this assessment

B8	x10^3/mm^3 ☐ Not Done	
B9	Hemoglobin (Hgb) at this assessment g/dl ☐ Not Done	
B10	Platelet count at this assessment x10^3/mm^3 ☐ Not Done	
C1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ○ -- ○ 1: Yes ○ 2: No	

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Donor Complications

Site ID:	310
Subject ID : Name	D4432 : xxxxx, xxxxx

The drop down list contains those complications we're tracking as part of the study.

A1	ComplicationType: --	
A2	Date of onset: Month Day Year	The onset date is the first date the complication is mentioned in the source documents. If the onset date is reported by the subject during a clinic visit, the information should be reported in the subject's chart.
A3	Ongoing? (•) -- ( ) 1: Yes ( ) 2: No	
A4	Date of resolution: Month Day Year	The resolution date is the date the complication is no longer mentioned in the source documents. If the resolution date is reported by the subject during a clinic visit, the information should be reported in the subject's chart.

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Hospitalization

Site ID:	902
Subject ID : Name	D4260 : M4vt0cuN, K2i/X0HK

Admissions less than 24 hours are not considered hospitalizations and should not be reported as such.

A1 Date of Admission:
Month Day Year

A2 Date of Discharge:
Month Day Year

A3 Was this admission associated with a study-tracked post-donation complication? (If yes, fill out Complication CRF.)
Refer to the MOO for the list of those complications being tracked in this study.
- (•) --
- ( ) 1: Yes
- ( ) 2: No

A4 Discharge Destination:
- (•) --
- ( ) 1: Home
- ( ) 2: Hospital-affiliated transitional residence
- ( ) 3: Transfer to another hospital
- ( ) 4: Rehabilitation facility
- ( ) 5: Nursing home
- ( ) 6: Other
- ( ) 7: N/A (patient died)

A5 Number of days in ICU (enter "0" for none, leave blank if unknown):
If a subject spends overnight in the PACU this is considered 1day in the ICU. If a subject spends overnight in the PACU and one day in the ICU this is considered 2 days in the ICU

A6 Type of hospital:
- (•) --
- ( ) 1: A2ALL hospital
- ( ) 2: Non-A2ALL hospital

A7 Type of hospital admission:
- (•) --
- ( ) 1: Liver donation operation
- ( ) 2: Post-donation complication
- ( ) 3: Post-donation other

A8 (For post-donation complication or post-donation other) Primary discharge diagnosis (enter numeric ICD-9/10 diagnosis code):
Add the primary reason for this hospital admission. Use the discharge diagnosis ICD9 code, if more than one separate by a comma

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

RCP Study Entry Information

Site ID:	310
Subject ID : Name	R4366 : zduJk/sS, KMyDXi/u

A1 Is recipient ranked as status 1 at time of enrollment?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

For GAP subjects the time of enrollment refers to the time prior to transplant. For prospective subjects the time point is the time of consent into the study.

A2 Recipient height at enrollment
_____ Inches

A3 Recipient weight at enrollment
_____ Pounds

A4 Recipient HIV results closest to date of enrollment
- (•) --
- ( ) 1: Positive
- ( ) 2: Negative
- ( ) 3: Cannot Disclose
- ( ) 998: Unknown

A5 Recipient Diagnoses: Please answer for each diagnosis.

Choose the diagnosis that best describes the reason for transplantation, may choose more than one.

Hepatitis C Virus Cirrhosis (HCV) — ICD 9 code = 070
- (•) --
- ( ) 1: Yes
- ( ) 2: No

Hepatocellular Carcinoma (HCC) — ICD 9 code = 155.0
- (•) --
- ( ) 1: Yes
- ( ) 2: No

Primary Hepatic Malignancy other than HCC — ICD 9 code = 199.1
- (•) --
- ( ) 1: Yes
- ( ) 2: No

Alcohol-related Cirrhosis — ICD 9 code = 571.2
- (•) --
- ( ) 1: Yes
- ( ) 2: No

Cryptogenic Cirrhosis — ICD 9 code = 571.5
- (•) --
- ( ) 1: Yes
- ( ) 2: No

PBC
ICD 9 code = 571.6
⊙ --
○ 1: Yes
○ 2: No

PSC
ICD 9 code = 576.1
⊙ --
○ 1: Yes
○ 2: No

Cirrhosis due to Autoimmune Hepatitis
ICD 9 code = 279.9
⊙ --
○ 1: Yes
○ 2: No

Hepatitis B Cirrhosis
ICD 9 code = 070.3
⊙ --
○ 1: Yes
○ 2: No

Cirrhosis due to Primary Hemochromatosis
ICD 9 code = 275.0
⊙ --
○ 1: Yes
○ 2: No

Acute Liver Failure (any etiology)
ICD 9 code = 570
⊙ --
○ 1: Yes
○ 2: No

Metabolic Liver Disease other than Primary Hemochromatosis
ICD 9 code = 277
⊙ --
○ 1: Yes
○ 2: No

Other Chronic Liver Disease/Cirrhosis
ICD 9 code = 571
⊙ --
○ 1: Yes
○ 2: No

A6 Recipient on dialysis at the time of enrollment
⊙ --
○ 1: Yes
○ 2: No

B1 Recipient serum creatinine closest to time of enrollment
[ ] mg/dl ☐ Not Done
For GAP subjects, labs here are those closest to the time of transplant.

B2 Recipient serum albumin closest to time of enrollment
[ ] g/dl ☐ Not Done

B3 Recipient total bilirubin closest to time of enrollment
[ ] mg/dl ☐ Not Done

B4 Recipient INR closest to time of enrollment
[ ] INR Units ☐ Not Done

B5 Serum AST closest to time of enrollment
[ ] IU/L ☐ Not Done

B6 Serum ALT closest to time of enrollment
[ ] IU/L ☐ Not Done

B7	Serum Alkaline Phosphatase (ALK) closest to time of enrollment IU/L ☐Not Done	
B8	Serum sodium closest to time of enrollment MEq/L ☐Not Done	
B9	Blood urea nitrogen (BUN) closest to time of enrollment mg/dl ☐Not Done	
B10	Hemoglobin (Hgb) closest to time of enrollment g/dl ☐Not Done	
B11	White blood count (WBC) closest to time of enrollment x10^3/mm^3 ☐Not Done	
B12	Platelet count closest to time of enrollment x10^3/mm^3 ☐Not Done	
C1	Date of imaging Month Day Year Imaging up to one year prior to transplant can be used.	
C2	Liver volume (CT or MR):	
C3	Spleen Volume (CT or MR):	
D1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed. Do not answer yes until all data elements have been completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ⊙-- ○1: Yes ○2: No	

Print

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Tasks

RCP Intraop

Site ID:	902
Subject ID : Name	R4162 : iL4dsBSO, q/EMkcDe

All source documents should contain all of the information entered on this eCRF. The PI is responsible for answering the anatomy and reconstruction questions and signing off on the intraoperative worksheet within 24 hours of the surgery. The date of surgery is linked to the date of the surgery entered on the subject dialog page, if it doesn't match, a warning will show.

A1 Date of transplant surgery:
Month Day Year

Please complete a hospitalization CRF for the transplant admission.

The ICD 9 code to be used on the hospitalization eCRF is the reason for transplantation. More than one code can be entered as long as they're separated by a comma.

B1 Recipient on ventilator at this assessment?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

B2 Recipient on dialysis at transplant?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

B3 Recipient weight closest to the time of transplant
Pounds

B4 Serum alanine aminotransferase (ALT) closest to the time of transplant
IU/L ☐ Not Done

If labs are not drawn at the time of transplant check not done for each, do not enter the same lab results that were entered on the Recipient Study Entry eCRF.

B5 Serum aspartate aminotransferase (AST) closest to the time of transplant
IU/L ☐ Not Done

B6 Serum alkaline phosphatase (ALK) closest to the time of transplant
IU/L ☐ Not Done

B7 Total bilirubin closest to the time of transplant
mg/dl ☐ Not Done

B8 Serum creatinine closest to the time of transplant
mg/dl ☐ Not Done

B9 Albumin closest to the time of transplant
g/dl ☐ Not Done

B10 INR closest to the time of transplant
INR Units ☐ Not Done

B11 Serum sodium closest to the time of transplant
MEq/L ☐ Not Done

B12 Blood urea nitrogen (BUN) closest to the time of transplant
mg/dl ☐ Not Done

B13 Hemoglobin (Hgb) closest to the time of transplant
g/dl ☐ Not Done

B14 White blood count (WBC) closest to the time of transplant
[ ] x10^3/mm^3 ☐ Not Done

B15 Platelet count closest to the time of transplant
[ ] x10^3/mm^3 ☐ Not Done

C1 Donor height closest to the time of donation:
[ ] Inches

The answers to C1 and C2 are linked to the DNR IntraOp questions B1 and B2, if they don't match a warning will show.

C2 Donor weight closest to the time of donation:
[ ] Pounds

C3 Was the transplant procedure aborted before completion? (if no, go to question C-4)
- ⊙ --
- ○ 1: Yes
- ○ 2: No

If yes to procedure abortion, why was the procedure aborted? (Check all that apply)
⊟ Click to Expand/Collapse
- ☐ Quality of donor liver
- ☐ Insufficient liver mass
- ☐ Technical difficulties in the donor
- ☐ Donor instability
- ☐ Unexpected medical findings in the recipient
- ☐ Recipient instability
- ☐ Recipient death on table
- ☐ Other

Specify "other" reason for procedure abortion:
[ ]

C4 Graft type:
[--]

This answer is linked to the DNR IntraOp eCRF question C9, if it doesn't match, a warning will show.

C5 What was the weight of the graft?
[ ] gm

This answer is linked to the DNR IntraOp eCRF question C11, if it doesn't match, a warning will show.

C6 Cross clamp time (24-hour clock time):
[ ]

This answer is linked to the DNR IntraOp eCRF question C17, if it doesn't match, a warning will show.

C7 Out of ice time (24-hour clock time):
[ ]

C8 Portal reperfusion time (24-hour clock time):
[ ]

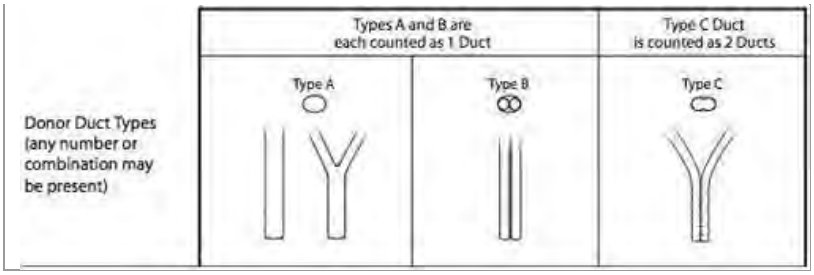
C9 Arterial reperfusion time (24-hour clock time):
[ ]

C10 Were any of the following medications used during the transplant procedure (intraoperatively or immediately post-operatively): Octreotide, Propanolol, or Vasopressin?
- ⊙ --
- ○ 1: Yes
- ○ 2: No

If yes, which medications were used (check all that apply)?
⊟
- ☐ Octreotide
- ☐ Propanolol
- ☐ Vasopressin

Choose the biliary reconstruction from the choices on the figure below:

D1

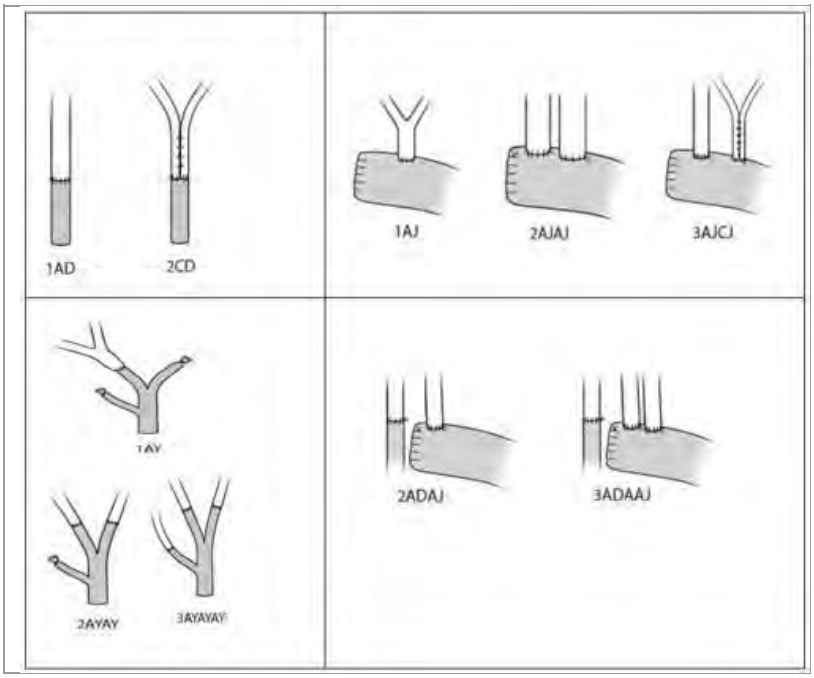


If the reconstruction doesn't match one of the drawings, choose the one that closely resembles the type performed and enter a comment in the comment text box.

- ⊙ --
- ○ 1: Type A
- ○ 2: Type B
- ○ 3: Type C
- ○ 4: More than 2 ducts

D2

Choose the biliary reconstruction type according to the figure below:



If the reconstruction doesn't match one of the drawings, choose the one that closely resembles the type performed and enter a comment in the comment text box.

-- ▾

D3

Was an accessory duct oversewn?

- ⊙ --
- ○ 1: Yes
- ○ 2: No

D4

Was a stent used in the reconstruction?

- ⊙ --
- ○ 1: Yes
- ○ 2: No

Hepatic venous reconstruction

D5

Was there back table ligation of any segmental veins?

- ⊙ --
- ○ 1: Yes
- ○ 2: No

D6

Was the middle hepatic vein included?

-- ▾

This answer is linked to the DNR IntraOp question C10, if it doesn't match, a warning will show.

Right lobe graft hepatic venous reconstruction (only answered if Right lobe graft):

D7

⊙ --
○ 1: Right vein includes all segments and anastomosed to vena cava
○ 2: Right vein anastomosed to vena cava and v6 anastomosed seperately
○ 3: Right vein anastomosed to vena cava plus V8 anastomosed to vena cava without interposition
○ 4: Right vein anastomosed to vena cava plus V8 anastomosed to vena cava with interposition
○ 5: Right vein anastomosed to vena cava plus V5 anastomosed to vena cava with interposition
○ 6: Right vein anastomosed to vena cava plus V5 and V8 anastomosed to vena cava with interposition
○ 7: V5, V6, V7, V8 anastomosed separately with interposition for V5 and V8

If yes to interposition graft, indicate the type of conduit used:

⊙ --
○ 1: Cryopreserved vessel
○ 2: Fresh homologous vessel
○ 3: Fresh autologous vessel
○ 4: PTFE conduit

D8

Left lobe graft hepatic venous reconstruction (only answered if Left lobe graft):

⊙ --
○ 1: Common orifice left and middle hepatic vein to recipient vena cava
○ 2: Common orifice left and middle hepatic vein to recipient common orifice of left and middle hepatic vein
○ 3: Separate implantation of left hepatic vein and middle hepatic vein to recipient vena cava

D9

Left lateral segment graft hepatic venous reconstruction (only answered if Left lateral segment graft):

⊙ --
○ 1: Left hepatic vein to recipient vena cava
○ 2: Left hepatic vein to recipient common orifice of left and middle hepatic vein

Portal Venous Reconstruction (All Grafts):

D10

Portal venous reconstruction:

⊙ --
○ 1: End-to-end
○ 2: Interposition graft

If yes to portal vein interposition graft, type of conduit used:

⊙ --
○ 1: Cryopreserved vessel
○ 2: Fresh homologous vessel
○ 3: Fresh autologous vessel
○ 4: PTFE conduit

Hepatic Artery Reconstruction (All Grafts):

D11

Number of hepatic arteries reconstructed:

⊙ --
○ 1: 1
○ 2: 2
○ 3: More than 2

Portal Vein Flow Modulation Information:

E1

Was surgical intraoperative portal vein flow modulation done? (if no skip to question E-6, otherwise please answer questions for each modulation procedure listed below)

This question is only answered yes if a surgical modulation was performed.

⊙ --
○ 1: Yes
○ 2: No

Was a splenectomy performed?

⊙ --

E2

- ○ 1: Yes - before reperfusion
- ○ 2: Yes - after reperfusion
- ○ 3: No

If yes, why was the modulation done? (check all that apply)

- ☐ Graft size
- ☐ Portal pressure
- ☐ Portal gradient
- ☐ Portal flow
- ☐ Arterial flow

E3

Was a splenic artery ligation performed?

- ⊙ --
- ○ 1: Yes - before reperfusion
- ○ 2: Yes - after reperfusion
- ○ 3: No

If yes, why was the modulation done? (check all that apply)

- ☐ Graft size
- ☐ Portal pressure
- ☐ Portal gradient
- ☐ Portal flow
- ☐ Arterial flow

E4

Was a portocaval shunt done?

- ⊙ --
- ○ 1: Yes - before reperfusion
- ○ 2: Yes - after reperfusion
- ○ 3: No

Shunt size: _____ mm

Shunt material:

- ⊙ --
- ○ 1: Cryopreserved vessel
- ○ 2: Native portal vein
- ○ 3: Fresh homologous vessel
- ○ 4: Fresh autologous vessel
- ○ 5: PTFE conduit

If yes, why was the modulation done? (check all that apply)

- ☐ Graft size
- ☐ Portal pressure
- ☐ Portal gradient
- ☐ Portal flow
- ☐ Arterial flow

E5

Was a collateral vein ligated as a portal vein flow modulation?

- ⊙ --
- ○ 1: Yes - before reperfusion
- ○ 2: Yes - after reperfusion
- ○ 3: No

If yes, why was the modulation done? (check all that apply)

- ☐ Graft size

- ☐ Portal pressure
- ☐ Portal gradient
- ☐ Portal flow
- ☐ Arterial flow

Pressure and Flow Measurements:
Document the flows and pressures below. Measurements should be performed in the native liver prior to removing the graft and then repeated after graft reperfusion. Flow measurements should be repeated after any portal flow modulation.

Native Liver Prior to Recipient Hepatectomy

E6 Hepatic artery flow (native liver):
- ⊙ --
- ○ Measured
- ○ Measured, not confident
- ○ Not measured

Mean: _____ ml/min

Minimum: _____ ml/min

Maximum: _____ ml/min

E7 Portal vein flow (native liver):
- ⊙ --
- ○ Measured
- ○ Measured, not confident
- ○ Not measured

Mean: _____ ml/min

Minimum: _____ ml/min

Maximum: _____ ml/min

E8 Clamped portal vein pressure (native liver): _____ 1: mmHg ☐ Not Done

E9 Unclamped portal vein pressure (native liver): _____ 1: mmHg ☐ Not Done

E10 Mean arterial pressure (native liver): _____ mmHg

E11 Central venous pressure (native liver): _____ mmHg

E12 Cardiac output (native liver): _____ L/min ☐ Not Done

Graft Immediately After Reperfusion

E14 Was any portal vein flow modulation done prior to reperfusion?
- ⊙ --
- ○ 1: Yes
- ○ 2: No

Any portal vein flow modulation refers to surgical or medical done prior to reperfusion.

Hepatic artery flow (after graft reperfusion):
- ⊙ --

E15
- Measured
- Measured, not confident
- Not measured

Mean: ml/min

Minimum: ml/min

Maximum: ml/min

E16 Portal vein flow (after graft reperfusion):
- --
- Measured
- Measured, not confident
- Not measured

Mean: ml/min

Minimum: ml/min

Maximum: ml/min

E17 Clamped portal vein pressure (after graft reperfusion): 1: mmHg Not Done

E18 Unclamped portal vein pressure (after graft reperfusion): 1: mmHg Not Done

E19 Mean arterial pressure (after graft reperfusion): mmHg

E20 Central venous pressure (after graft reperfusion): mmHg

E21 Cardiac output (after graft reperfusion): L/min Not Done

E22 Were any post-reperfusion portal vein modulations performed?
- --
- 1: Yes
- 2: No

If yes, how many post-reperfusion portal vein modulations were performed? (Please fill out the pressure and flow measurements for each modulation.)
- --
- 1
- 2
- 3
- 4

After Post-Reperfustion Portal Vein Flow Modulation #1

E23 Type of portal vein modulation performed:
- --
- 1: Medical modulation
- 2: Splenic artery ligation
- 3: Collateral vein ligation
- 4: Portocaval shunt

	○ 5: Splenectomy	
E24	Hepatic artery flow (after modulation 1): ⊙ -- ○ Measured ○ Measured, not confident ○ Not measured	
	Mean: _____ ml/min	
	Minimum: _____ ml/min	
	Maximum: _____ ml/min	
E25	Portal vein flow (after modulation 1): ⊙ -- ○ Measured ○ Measured, not confident ○ Not measured	
	Mean: _____ ml/min	
	Minimum: _____ ml/min	
	Maximum: _____ ml/min	
E26	Clamped portal vein pressure (after modulation 1): _____ 1: mmHg ☐ Not Done	
E27	Unclamped portal vein pressure (after modulation 1): _____ 1: mmHg ☐ Not Done	
E28	Mean arterial pressure (after modulation 1): _____ mmHg	
E29	Central venous pressure (after modulation 1): _____ mmHg	
E30	Cardiac output (after modulation 1): _____ L/min ☐ Not Done	
	After Post-Reperfustion Portal Vein Flow Modulation #2	
E31	Type of portal vein modulation performed: ⊙ -- ○ 1: Medical modulation ○ 2: Splenic artery ligation ○ 3: Collateral vein ligation ○ 4: Portocaval shunt ○ 5: Splenectomy	
E32	Hepatic artery flow (after modulation 2): ⊙ -- ○ Measured ○ Measured, not confident ○ Not measured	
	Mean:	

ml/min

Minimum:
ml/min

Maximum:
ml/min

E33 Portal vein flow (after modulation 2):
- ⊙ --
- ○ Measured
- ○ Measured, not confident
- ○ Not measured

Mean:
ml/min

Minimum:
ml/min

Maximum:
ml/min

E34 Clamped portal vein pressure (after modulation 2):
1: mmHg ☐ Not Done

E35 Unclamped portal vein pressure (after modulation 2):
1: mmHg ☐ Not Done

E36 Mean arterial pressure (after modulation 2):
mmHg

E37 Central venous pressure (after modulation 2):
mmHg

E38 Cardiac output (after modulation 2):
L/min ☐ Not Done

After Post-Reperfustion Portal Vein Flow Modulation #3

E39 Type of portal vein modulation performed:
- ⊙ --
- ○ 1: Medical modulation
- ○ 2: Splenic artery ligation
- ○ 3: Collateral vein ligation
- ○ 4: Portocaval shunt
- ○ 5: Splenectomy

E40 Hepatic artery flow (after modulation 3):
- ⊙ --
- ○ Measured
- ○ Measured, not confident
- ○ Not measured

Mean:
ml/min

Minimum:
ml/min

Maximum:
ml/min

Portal vein flow (after modulation 3):
- ⊙ --

E41
- Measured
- Measured, not confident
- Not measured

Mean: ml/min

Minimum: ml/min

Maximum: ml/min

E42 Clamped portal vein pressure (after modulation 3): 1: mmHg Not Done

E43 Unclamped portal vein pressure (after modulation 3): 1: mmHg Not Done

E44 Mean arterial pressure (after modulation 3): mmHg

E45 Central venous pressure (after modulation 3): mmHg

E46 Cardiac output (after modulation 3): L/min Not Done

After Post-Reperfustion Portal Vein Flow Modulation #4

E47 Type of portal vein modulation performed:
- --
- 1: Medical modulation
- 2: Splenic artery ligation
- 3: Collateral vein ligation
- 4: Portocaval shunt
- 5: Splenectomy

E48 Hepatic artery flow (after modulation 4):
- --
- Measured
- Measured, not confident
- Not measured

Mean: ml/min

Minimum: ml/min

Maximum: ml/min

E49 Portal vein flow (after modulation 4):
- --
- Measured
- Measured, not confident
- Not measured

Mean: ml/min

Minimum: ml/min

	Maximum: ml/min	
E50	Clamped portal vein pressure (after modulation 4): 1: mmHg Not Done	
E51	Unclamped portal vein pressure (after modulation 4): 1: mmHg Not Done	
E52	Mean arterial pressure (after modulation 4): mmHg	
E53	Central venous pressure (after modulation 4): mmHg	
E54	Cardiac output (after modulation 4): L/min Not Done	
F1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): (•) -- ( ) 1: Yes ( ) 2: No	

eCRF revised 10252012
Annotation revised 07232012

Print

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Tasks

HCC Explant Assessment

Site ID:	902

Subject ID : Name	R4614 : 5aVOttwz, Ppkx9Qw9

This form is completed only when a recipient has a pre-txp diagnosis of HCC or when there's an incidental finding of HCC on the explant.

A1 What did the HCC explant assessment reveal?
- (•) --
- ( ) 1: Confirmation of pre-liver transplant HCC Diagnosis
- ( ) 2: HCC was not present
- ( ) 3: Incidental (not known pre-transplant) HCC found

A2 HCC location
- (•) --
- ( ) 1: Right lobe only
- ( ) 2: Left lobe only
- ( ) 3: Bilobar

A3 Number of HCC nodules in the liver
- (•) --
- ( ) 1: 1
- ( ) 2: 2
- ( ) 3: 3
- ( ) 4: 4
- ( ) 5: 5
- ( ) 6: 6+

Describe Nodule 1

A4 Size of Nodule 1 [ ] cm

A5 Was there tumor invasion into vascular structures?
- (•) --
- ( ) 1: No
- ( ) 2: Micro invasion: micrometer tumor invasion into the portal or hepatic vein
- ( ) 3: Macro invasion: millimeter tumor invasion into the portal or hepatic vein
- ( ) 998: Unknown/not assessed

A6 Tumor grade
- (•) --
- ( ) 1: G1: well-differentiated
- ( ) 2: G2: moderately differentiated
- ( ) 3: G3: poorly differentiated
- ( ) 998: Unknown/not assessed

A7 What level of mitosis was observed on microscopic analysis?
- (•) --
- ( ) 1: < 10 HPF

	○ 2: >= 10 HPF ○ 998: Unknown	
A8	Proportion of tumor necrosis ⊙ -- ○ 1: 0% ○ 2: 1%-25% ○ 3: 26%-50% ○ 4: 51%-75% ○ 5: 76%-100% ○ 998: Unknown	
	Describe Nodule 2	
A9	Size of Nodule 2 [ ] cm	
A10	Was there tumor invasion into vascular structures? ⊙ -- ○ 1: No ○ 2: Micro invasion: micrometer tumor invasion into the portal or hepatic vein ○ 3: Macro invasion: millimeter tumor invasion into the portal or hepatic vein ○ 998: Unknown/not assessed	
A11	Tumor grade ⊙ -- ○ 1: G1: well-differentiated ○ 2: G2: moderately differentiated ○ 3: G3: poorly differentiated ○ 998: Unknown/not assessed	
A12	What level of mitosis was observed on microscopic analysis? ⊙ -- ○ 1: < 10 HPF ○ 2: >= 10 HPF ○ 998: Unknown	
A13	Proportion of tumor necrosis ⊙ -- ○ 1: 0% ○ 2: 1%-25% ○ 3: 26%-50% ○ 4: 51%-75% ○ 5: 76%-100% ○ 998: Unknown	
	Describe Nodule 3	
A14	Size of Nodule 3 [ ] cm	
A15	Was there tumor invasion into vascular structures? ⊙ -- ○ 1: No ○ 2: Micro invasion: micrometer tumor invasion into the portal or hepatic vein ○ 3: Macro invasion: millimeter tumor invasion into the portal or hepatic vein ○ 998: Unknown/not assessed	
	Tumor grade ⊙ --	

A16	○ 1: G1: well-differentiated ○ 2: G2: moderately differentiated ○ 3: G3: poorly differentiated ○ 998: Unknown/not assessed	
A17	What level of mitosis was observed on microscopic analysis? ⊙ -- ○ 1: < 10 HPF ○ 2: >= 10 HPF ○ 998: Unknown	
A18	Proportion of tumor necrosis ⊙ -- ○ 1: 0% ○ 2: 1%-25% ○ 3: 26%-50% ○ 4: 51%-75% ○ 5: 76%-100% ○ 998: Unknown	
	Describe Nodule 4	
A19	Size of Nodule 4 _____ cm	
A20	Was there tumor invasion into vascular structures? ⊙ -- ○ 1: No ○ 2: Micro invasion: micrometer tumor invasion into the portal or hepatic vein ○ 3: Macro invasion: millimeter tumor invasion into the portal or hepatic vein ○ 998: Unknown/not assessed	
A21	Tumor grade ⊙ -- ○ 1: G1: well-differentiated ○ 2: G2: moderately differentiated ○ 3: G3: poorly differentiated ○ 998: Unknown/not assessed	
A22	What level of mitosis was observed on microscopic analysis? ⊙ -- ○ 1: < 10 HPF ○ 2: >= 10 HPF ○ 998: Unknown	
A23	Proportion of tumor necrosis ⊙ -- ○ 1: 0% ○ 2: 1%-25% ○ 3: 26%-50% ○ 4: 51%-75% ○ 5: 76%-100% ○ 998: Unknown	
	Describe Nodule 5	
A24	Size of Nodule 5 _____ cm	

A25 Was there tumor invasion into vascular structures?
- ⊙ --
- ○ 1: No
- ○ 2: Micro invasion: micrometer tumor invasion into the portal or hepatic vein
- ○ 3: Macro invasion: millimeter tumor invasion into the portal or hepatic vein
- ○ 998: Unknown/not assessed

A26 Tumor grade
- ⊙ --
- ○ 1: G1: well-differentiated
- ○ 2: G2: moderately differentiated
- ○ 3: G3: poorly differentiated
- ○ 998: Unknown/not assessed

A27 What level of mitosis was observed on microscopic analysis?
- ⊙ --
- ○ 1: < 10 HPF
- ○ 2: >= 10 HPF
- ○ 998: Unknown

A28 Proportion of tumor necrosis
- ⊙ --
- ○ 1: 0%
- ○ 2: 1%-25%
- ○ 3: 26%-50%
- ○ 4: 51%-75%
- ○ 5: 76%-100%
- ○ 998: Unknown

Describe Nodule 6

A29 Size of Nodule 6 _____ cm

A30 Was there tumor invasion into vascular structures?
- ⊙ --
- ○ 1: No
- ○ 2: Micro invasion: micrometer tumor invasion into the portal or hepatic vein
- ○ 3: Macro invasion: millimeter tumor invasion into the portal or hepatic vein
- ○ 998: Unknown/not assessed

A31 Tumor grade
- ⊙ --
- ○ 1: G1: well-differentiated
- ○ 2: G2: moderately differentiated
- ○ 3: G3: poorly differentiated
- ○ 998: Unknown/not assessed

A32 What level of mitosis was observed on microscopic analysis?
- ⊙ --
- ○ 1: < 10 HPF
- ○ 2: >= 10 HPF
- ○ 998: Unknown

A33 Proportion of tumor necrosis
- ⊙ --
- ○ 1: 0%
- ○ 2: 1%-25%
- ○ 3: 26%-50%

	○ 4: 51%-75% ○ 5: 76%-100% ○ 998: Unknown	
B1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ⊙ -- ○ 1: Yes ○ 2: No	

eCRF revised 06292012

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Post-Txp Week 1 Assessment

Site ID:	902

Subject ID : Name	R4162 : iL4dsBSO, q/EMkcDe

Visit window for Week 1 is Txp day through Day 10

A1 Date of contact:

Month Day Year

A2 What is the recipient's current status? (if dead, enter death information on subject page)

- --
- 1: Alive
- 2: Dead
- 998: Unknown

A3 What is the status of the liver graft? (if failed, enter retransplant date and cause of graft failure on subject page)

- --
- 1: Functional
- 2: Failed
- 3: Unknown

A4 Did the patient have a biopsy performed since the last assessment? (if yes, fill out biopsy report CRF)

- --
- 1: Yes
- 2: No

This includes all "for cause" biopsies as well as those for HCV pre and post treatment.
For all biopsies performed a post-transplant biopsy report must be completed.

A5 Has the patient been re-hospitalized since the transplant procedure? (If so, fill out Hospitalization CRF.)

- --
- 1: Yes
- 2: No

A6 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)

- --
- 1: Yes
- 2: No

A7 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)

- --
- 1: Yes
- 2: No

A8 Recipient medical condition at this assessment.

- --
- 1: Patient in ICU
- 2: Hospitalized, not in ICU
- 3: In rehab facility
- 4: Not hospitalized

Recipient on ventilator at this assessment?

A9

- --
- 1: Yes
- 2: No
- 998: Unknown

A10

What was the immunosuppression regimen in place during this assessment? (Check all that apply)

Click to Expand/Collapse

- ☐ Prednisone (or oral equivalent)
- ☐ Methylprednisolone (or IV equivalent)
- ☐ Cyclosporine (Neoral, Gengraf or any other formulation)
- ☐ Tacrolimus (Prograf)
- ☐ Rapamycin (Sirolimus, Rapamune)
- ☐ Certican (RAD) (Everolimus)
- ☐ Azathioprine (Imuran or generic)
- ☐ Mycophenolate mofetil (Cellcept or generic)
- ☐ Enteric-coated mycophenolic (Myfortic or generic)
- ☐ Other immunosuppression (specify)

Specify "other" immunosuppression:

A11

Did the patient have a rejection episode that was confirmed by a biopsy since the last assessment?

A post-transplant biopsy report must be completed for each biopsy performed.

- --
- 1: Yes
- 2: No

If yes, how many biopsy-proven rejection episodes has the patient had since the last assessment?

A12

Recipient on dialysis at this assessment?

- --
- 1: No
- 2: Hemodialysis/CVVHD
- 3: Peritoneal Dialysis
- 4: Dialysis - Unknown Type
- 998: Unknown

B1

Was portal vein flow modulation performed after the recipient transplant operation?

- --
- 1: Yes
- 2: No

B2

Was the patient returned to the operating room for a splenectomy?

- --
- 1: Yes
- 2: No

B3

Was the patient returned to the operating room for splenic artery ligation?

- --
- 1: Yes
- 2: No

B4

Was the patient returned to the operating room for portocaval shunt?

- --
- 1: Yes
- 2: No

Shunt size: mm

Shunt material:

	○ -- ○ 1: Cryopreserved vessel ○ 2: Native portal vein ○ 3: Fresh homologous vessel ○ 4: Fresh autologous vessel ○ 5: PTFE conduit	
B5	Was the patient returned to the operating room for collateral vein ligation? ○ -- ○ 1: Yes ○ 2: No	
B6	Was medical modulation started for the first time post-operatively? Answer “No” if it was started during the original transplant operation. ○ -- ○ 1: Yes ○ 2: No	
	If yes, what medical modulation was used? (check all that apply) ☐ Octreotide ☐ Propanolol ☐ Vasopressin	
	Specify "other" medical modulation:	
C1	Serum alanine aminotransferase (ALT) at this assessment IU/L ☐ Not Done	
C2	Serum aspartate aminotransferase (AST) at this assessment IU/L ☐ Not Done	
C3	Serum alkaline phosphatase (ALK) at this assessment IU/L ☐ Not Done	
C4	Total serum bilirubin at this assessment mg/dl ☐ Not Done	
C5	Serum sodium at this assessment MEq/L ☐ Not Done	
C6	Serum creatinine at this assessment mg/dl ☐ Not Done	
C7	Total serum albumin at this assessment g/dl ☐ Not Done	
C8	INR at this assessment INR Units ☐ Not Done	
C9	Blood Urea Nitrogen (BUN) at this assessment mg/dl ☐ Not Done	
C10	Hemoglobin (Hgb) at this assessment g/dl ☐ Not Done	
C11	White blood count (WBC) at this assessment x10^3/mm^3 ☐ Not Done	
C12	Platelet count at this assessment x10^3/mm^3 ☐ Not Done	
C13	Did the patient have a drain in place at this assessment? ○ --	Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

1: Yes
2: No

Drain output at this assessment
_____ L/24 hrs ☐ Not Done

C14
Degree of hepatic encephalopathy:
Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.
--
0: None
1: Subject intubated/sedated - unable to assess
2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
6: Subject is not in hospital - unable to assess

D1
Ultrasound Doppler: Post-op day 1 portal velocity:
_____ cm/sec

E1
Serum alanine aminotransferase (ALT) at this assessment
_____ IU/L ☐ Not Done

E2
Serum aspartate aminotransferase (AST) at this assessment
_____ IU/L ☐ Not Done

E3
Serum alkaline phosphatase (ALK) at this assessment
_____ IU/L ☐ Not Done

E4
Total serum bilirubin at this assessment
_____ mg/dl ☐ Not Done

E5
Serum sodium at this assessment
_____ MEq/L ☐ Not Done

E6
Serum creatinine at this assessment
_____ mg/dl ☐ Not Done

E7
Total serum albumin at this assessment
_____ g/dl ☐ Not Done

E8
INR at this assessment
_____ INR Units ☐ Not Done

E9
Blood Urea Nitrogen (BUN) at this assessment
_____ mg/dl ☐ Not Done

E10
Hemoglobin (Hgb) at this assessment
_____ g/dl ☐ Not Done

E11
White blood count (WBC) at this assessment
_____ x10^3/mm^3 ☐ Not Done

E12
Platelet count at this assessment
_____ x10^3/mm^3 ☐ Not Done

E13
Did the patient have a drain in place at this assessment?
Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.
--
1: Yes
2: No

Drain output at this assessment
_____ L/24 hrs ☐ Not Done

Degree of hepatic encephalopathy:
Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.
--

E14
- 0: None
- 1: Subject intubated/sedated - unable to assess
- 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
- 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
- 6: Subject is not in hospital - unable to assess

F1 Serum alanine aminotransferase (ALT) at this assessment
IU/L Not Done

F2 Serum aspartate aminotransferase (AST) at this assessment
IU/L Not Done

F3 Serum alkaline phosphatase (ALK) at this assessment
IU/L Not Done

F4 Total serum bilirubin at this assessment
mg/dl Not Done

F5 Serum sodium at this assessment
MEq/L Not Done

F6 Serum creatinine at this assessment
mg/dl Not Done

F7 Total serum albumin at this assessment
g/dl Not Done

F8 INR at this assessment
INR Units Not Done

F9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl Not Done

F10 Hemoglobin (Hgb) at this assessment
g/dl Not Done

F11 White blood count (WBC) at this assessment
x10^3/mm^3 Not Done

F12 Platelet count at this assessment
x10^3/mm^3 Not Done

F13 Did the patient have a drain in place at this assessment?
- --
- 1: Yes
- 2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs Not Done

F14 Degree of hepatic encephalopathy:
- --
- 0: None
- 1: Subject intubated/sedated - unable to assess
- 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
- 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
- 6: Subject is not in hospital - unable to assess

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

Were Day 4 Labs Done?
- --

Yes
No

G1 Serum alanine aminotransferase (ALT) at this assessment
IU/L Not Done

G2 Serum aspartate aminotransferase (AST) at this assessment
IU/L Not Done

G3 Serum alkaline phosphatase (ALK) at this assessment
IU/L Not Done

G4 Total serum bilirubin at this assessment
mg/dl Not Done

G5 Serum sodium at this assessment
MEq/L Not Done

G6 Serum creatinine at this assessment
mg/dl Not Done

G7 Total serum albumin at this assessment
g/dl Not Done

G8 INR at this assessment
INR Units Not Done

G9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl Not Done

G10 Hemoglobin (Hgb) at this assessment
g/dl Not Done

G11 White blood count (WBC) at this assessment
x10^3/mm^3 Not Done

G12 Platelet count at this assessment
x10^3/mm^3 Not Done

G13 Did the patient have a drain in place at this assessment?
--
1: Yes
2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs Not Done

G14 Degree of hepatic encephalopathy:
--
0: None
1: Subject intubated/sedated - unable to assess
2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
6: Subject is not in hospital - unable to assess

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

Were Day 5 Labs Done?
--
Yes
No

H1 Serum alanine aminotransferase (ALT) at this assessment
IU/L Not Done

H2 Serum aspartate aminotransferase (AST) at this assessment
IU/L ☐ Not Done

H3 Serum alkaline phosphatase (ALK) at this assessment
IU/L ☐ Not Done

H4 Total serum bilirubin at this assessment
mg/dl ☐ Not Done

H5 Serum sodium at this assessment
MEq/L ☐ Not Done

H6 Serum creatinine at this assessment
mg/dl ☐ Not Done

H7 Total serum albumin at this assessment
g/dl ☐ Not Done

H8 INR at this assessment
INR Units ☐ Not Done

H9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl ☐ Not Done

H10 Hemoglobin (Hgb) at this assessment
g/dl ☐ Not Done

H11 White blood count (WBC) at this assessment
x10^3/mm^3 ☐ Not Done

H12 Platelet count at this assessment
x10^3/mm^3 ☐ Not Done

H13 Did the patient have a drain in place at this assessment?
- --
- 1: Yes
- 2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs ☐ Not Done

H14 Degree of hepatic encephalopathy:
- --
- 0: None
- 1: Subject intubated/sedated - unable to assess
- 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
- 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
- 6: Subject is not in hospital - unable to assess

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

Were Day 6 Labs Done?
- --
- Yes
- No

I1 Serum alanine aminotransferase (ALT) at this assessment
IU/L ☐ Not Done

I2 Serum aspartate aminotransferase (AST) at this assessment
IU/L ☐ Not Done

I3 Serum alkaline phosphatase (ALK) at this assessment
IU/L ☐ Not Done

I4 Total serum bilirubin at this assessment
mg/dl ☐ Not Done

I5 Serum sodium at this assessment
MEq/L ☐ Not Done

I6 Serum creatinine at this assessment
mg/dl ☐ Not Done

I7 Total serum albumin at this assessment
g/dl ☐ Not Done

I8 INR at this assessment
INR Units ☐ Not Done

I9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl ☐ Not Done

I10 Hemoglobin (Hgb) at this assessment
g/dl ☐ Not Done

I11 White blood count (WBC) at this assessment
x10^3/mm^3 ☐ Not Done

I12 Platelet count at this assessment
x10^3/mm^3 ☐ Not Done

I13 Did the patient have a drain in place at this assessment?
- --
- 1: Yes
- 2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs ☐ Not Done

I14 Degree of hepatic encephalopathy:
- --
- 0: None
- 1: Subject intubated/sedated - unable to assess
- 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
- 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
- 6: Subject is not in hospital - unable to assess

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

J1 Recipient weight at this assessment
Pounds ☐ Not Done

J2 Serum alanine aminotransferase (ALT) at this assessment
IU/L ☐ Not Done

J3 Serum aspartate aminotransferase (AST) at this assessment
IU/L ☐ Not Done

J4 Serum alkaline phosphatase (ALK) at this assessment
IU/L ☐ Not Done

J5 Total serum bilirubin at this assessment
mg/dl ☐ Not Done

J6 Serum sodium at this assessment
MEq/L ☐ Not Done

J7 Serum creatinine at this assessment
mg/dl ☐ Not Done

J8 Total serum albumin at this assessment
g/dl Not Done

J9 INR at this assessment
INR Units Not Done

J10 Blood Urea Nitrogen (BUN) at this assessment
mg/dl Not Done

J11 Hemoglobin (Hgb) at this assessment
g/dl Not Done

J12 White blood count (WBC) at this assessment
x10^3/mm^3 Not Done

J13 Platelet count at this assessment
x10^3/mm^3 Not Done

J14 Did the patient have a drain in place at this assessment?
- --
- 1: Yes
- 2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs Not Done

J15 Degree of hepatic encephalopathy:
- --
- 0: None
- 1: Subject intubated/sedated - unable to assess
- 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
- 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
- 6: Subject is not in hospital - unable to assess

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

J16 In the opinion of the PI, did the subject have small for size syndrome (SFSS)?
- --
- 1: Yes
- 2: No

The opinion of the principal investigator must be well documented/sourced. The DCC provides a source document for your use.

J17 If the subject had SFSS, did the subject also have any of the following vascular and/or biliary complications: 1. Thrombosis or stenosis of the portal vein, hepatic artery, and/or the hepatic vein 2. Bile leak and/or stricture
- --
- 1: Yes
- 2: No

K1 Questionnaire Completed

Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.

This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC):
- --
- 1: Yes
- 2: No

eCRF revised 06102013
Annotation revised 07222013

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Post-Txp Week 2 Assessment

Site ID:	902

Subject ID : Name	R4162 : iL4dsBSO, q/EMkcDe

A1 Date of contact: ____ ____ ____ (Month Day Year)

The visit window for the Week 2 Assessment is Day 11 to Day 22

A2 What is the recipient's current status? (if dead, enter death information on subject page)
- --
- 1: Alive
- 2: Dead
- 998: Unknown

A3 What is the status of the liver graft? (if failed, enter retransplant date and cause of graft failure on subject page)
- --
- 1: Functional
- 2: Failed
- 3: Unknown

A4 Did the patient have a biopsy performed since the last assessment? (if yes, fill out biopsy report CRF)
- --
- 1: Yes
- 2: No

This includes all "for cause" biopsies as well as those for HCV pre and post treatment.
For each biopsy performed a post-transplant biopsy report must be completed.

A5 Has the patient been hospitalized since the last assessment? (If yes, fill out Hospitalization CRF.)
- --
- 1: Yes
- 2: No

A6 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)
- --
- 1: Yes
- 2: No

A7 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)
- --
- 1: Yes
- 2: No

A8 Recipient medical condition at this assessment.
- --
- 1: Patient in ICU
- 2: Hospitalized, not in ICU
- 3: In rehab facility
- 4: Not hospitalized

Recipient on ventilator at this assessment?

A9
- --
- 1: Yes
- 2: No
- 998: Unknown

A10
What was the immunosuppression regimen in place during this assessment? (Check all that apply)

Click to Expand/Collapse

- ☐ Prednisone (or oral equivalent)
- ☐ Methylprednisolone (or IV equivalent)
- ☐ Cyclosporine (Neoral, Gengraf or any other formulation)
- ☐ Tacrolimus (Prograf)
- ☐ Rapamycin (Sirolimus, Rapamune)
- ☐ Certican (RAD) (Everolimus)
- ☐ Azathioprine (Imuran or generic)
- ☐ Mycophenolate mofetil (Cellcept or generic)
- ☐ Enteric-coated mycophenolic (Myfortic or generic)
- ☐ Other immunosuppression (specify)

Specify "other" immunosuppression:

A11
Did the patient have a rejection episode that was confirmed by a biopsy since the last assessment?

For each biopsy performed a post-transplant biopsy report must be completed.

- --
- 1: Yes
- 2: No

If yes, how many biopsy-proven rejection episodes has the patient had since the last assessment?

A12
Recipient on dialysis at this assessment?
- --
- 1: No
- 2: Hemodialysis/CVVHD
- 3: Peritoneal Dialysis
- 4: Dialysis - Unknown Type
- 998: Unknown

A13
Was HCC an incidental finding on the explant pathology form?
- --
- 1: Yes (complete HCC Explant CRF)
- 2: No
- 3: Not Applicable (subject had pre-transplant HCC diagnosis, complete HCC Explant CRF)

Were Day 8 Labs Done?
- --
- Yes
- No

B1
Serum alanine aminotransferase (ALT) at this assessment
IU/L ☐ Not Done

B2
Serum aspartate aminotransferase (AST) at this assessment
IU/L ☐ Not Done

B3
Serum alkaline phosphatase (ALK) at this assessment
IU/L ☐ Not Done

B4
Total serum bilirubin at this assessment
mg/dl ☐ Not Done

B5
Serum sodium at this assessment
MEq/L ☐ Not Done

B6 Serum creatinine at this assessment
mg/dl Not Done

B7 Total serum albumin at this assessment
g/dl Not Done

B8 INR at this assessment
INR Units Not Done

B9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl Not Done

B10 Hemoglobin (Hgb) at this assessment
g/dl Not Done

B11 White blood count (WBC) at this assessment
x10^3/mm^3 Not Done

B12 Platelet count at this assessment
x10^3/mm^3 Not Done

B13 Did the patient have a drain in place at this assessment?
-- 1: Yes 2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs Not Done

B14 Degree of hepatic encephalopathy:
--
0: None
1: Subject intubated/sedated - unable to assess
2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
6: Subject is not in hospital - unable to assess

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

Were Day 9 Labs Done?
-- Yes No

C1 Serum alanine aminotransferase (ALT) at this assessment
IU/L Not Done

C2 Serum aspartate aminotransferase (AST) at this assessment
IU/L Not Done

C3 Serum alkaline phosphatase (ALK) at this assessment
IU/L Not Done

C4 Total serum bilirubin at this assessment
mg/dl Not Done

C5 Serum sodium at this assessment
MEq/L Not Done

C6 Serum creatinine at this assessment
mg/dl Not Done

C7 Total serum albumin at this assessment
g/dl Not Done

C8 INR at this assessment
INR Units ☐ Not Done

C9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl ☐ Not Done

C10 Hemoglobin (Hgb) at this assessment
g/dl ☐ Not Done

C11 White blood count (WBC) at this assessment
x10^3/mm^3 ☐ Not Done

C12 Platelet count at this assessment
x10^3/mm^3 ☐ Not Done

C13 Did the patient have a drain in place at this assessment?
○ --
○ 1: Yes
○ 2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs ☐ Not Done

C14 Degree of hepatic encephalopathy:
○ --
○ 0: None
○ 1: Subject intubated/sedated - unable to assess
○ 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
○ 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
○ 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
○ 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
○ 6: Subject is not in hospital - unable to assess

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

Were Day 10 Labs Done?
○ --
○ Yes
○ No

D1 Serum alanine aminotransferase (ALT) at this assessment
IU/L ☐ Not Done

D2 Serum aspartate aminotransferase (AST) at this assessment
IU/L ☐ Not Done

D3 Serum alkaline phosphatase (ALK) at this assessment
IU/L ☐ Not Done

D4 Total serum bilirubin at this assessment
mg/dl ☐ Not Done

D5 Serum sodium at this assessment
MEq/L ☐ Not Done

D6 Serum creatinine at this assessment
mg/dl ☐ Not Done

D7 Total serum albumin at this assessment
g/dl ☐ Not Done

D8 INR at this assessment
INR Units ☐ Not Done

D9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl ☐ Not Done

D10 Hemoglobin (Hgb) at this assessment
g/dl Not Done

D11 White blood count (WBC) at this assessment
x10^3/mm^3 Not Done

D12 Platelet count at this assessment
x10^3/mm^3 Not Done

D13 Did the patient have a drain in place at this assessment?
-- 1: Yes 2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs Not Done

D14 Degree of hepatic encephalopathy:
-- 0: None 1: Subject intubated/sedated - unable to assess 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior. 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation. 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli). 6: Subject is not in hospital - unable to assess

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

Were Day 11 Labs Done?
-- Yes No

E1 Serum alanine aminotransferase (ALT) at this assessment
IU/L Not Done

E2 Serum aspartate aminotransferase (AST) at this assessment
IU/L Not Done

E3 Serum alkaline phosphatase (ALK) at this assessment
IU/L Not Done

E4 Total serum bilirubin at this assessment
mg/dl Not Done

E5 Serum sodium at this assessment
MEq/L Not Done

E6 Serum creatinine at this assessment
mg/dl Not Done

E7 Total serum albumin at this assessment
g/dl Not Done

E8 INR at this assessment
INR Units Not Done

E9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl Not Done

E10 Hemoglobin (Hgb) at this assessment
g/dl Not Done

E11 White blood count (WBC) at this assessment
x10^3/mm^3 Not Done

E12 Platelet count at this assessment
[ ] x10^3/mm^3 ☐ Not Done

E13 Did the patient have a drain in place at this assessment?
Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.
- --
- 1: Yes
- 2: No

Drain output at this assessment
[ ] L/24 hrs ☐ Not Done

E14 Degree of hepatic encephalopathy:
Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.
- --
- 0: None
- 1: Subject intubated/sedated - unable to assess
- 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
- 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
- 6: Subject is not in hospital - unable to assess

Were Day 12 Labs Done?
- --
- Yes
- No

F1 Serum alanine aminotransferase (ALT) at this assessment
[ ] IU/L ☐ Not Done

F2 Serum aspartate aminotransferase (AST) at this assessment
[ ] IU/L ☐ Not Done

F3 Serum alkaline phosphatase (ALK) at this assessment
[ ] IU/L ☐ Not Done

F4 Total serum bilirubin at this assessment
[ ] mg/dl ☐ Not Done

F5 Serum sodium at this assessment
[ ] MEq/L ☐ Not Done

F6 Serum creatinine at this assessment
[ ] mg/dl ☐ Not Done

F7 Total serum albumin at this assessment
[ ] g/dl ☐ Not Done

F8 INR at this assessment
[ ] INR Units ☐ Not Done

F9 Blood Urea Nitrogen (BUN) at this assessment
[ ] mg/dl ☐ Not Done

F10 Hemoglobin (Hgb) at this assessment
[ ] g/dl ☐ Not Done

F11 White blood count (WBC) at this assessment
[ ] x10^3/mm^3 ☐ Not Done

F12 Platelet count at this assessment
[ ] x10^3/mm^3 ☐ Not Done

F13 Did the patient have a drain in place at this assessment?
Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.
- --
- 1: Yes

2: No

Drain output at this assessment
L/24 hrs Not Done

F14

Degree of hepatic encephalopathy:

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

--
0: None
1: Subject intubated/sedated - unable to assess
2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
6: Subject is not in hospital - unable to assess

Were Day 13 Labs Done?
--
Yes
No

G1 Serum alanine aminotransferase (ALT) at this assessment
IU/L Not Done

G2 Serum aspartate aminotransferase (AST) at this assessment
IU/L Not Done

G3 Serum alkaline phosphatase (ALK) at this assessment
IU/L Not Done

G4 Total serum bilirubin at this assessment
mg/dl Not Done

G5 Serum sodium at this assessment
MEq/L Not Done

G6 Serum creatinine at this assessment
mg/dl Not Done

G7 Total serum albumin at this assessment
g/dl Not Done

G8 INR at this assessment
INR Units Not Done

G9 Blood Urea Nitrogen (BUN) at this assessment
mg/dl Not Done

G10 Hemoglobin (Hgb) at this assessment
g/dl Not Done

G11 White blood count (WBC) at this assessment
x10^3/mm^3 Not Done

G12 Platelet count at this assessment
x10^3/mm^3 Not Done

G13

Did the patient have a drain in place at this assessment?

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

--
1: Yes
2: No

Drain output at this assessment
L/24 hrs Not Done

Degree of hepatic encephalopathy:

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

G14

- --
- 0: None
- 1: Subject intubated/sedated - unable to assess
- 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.
- 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli).
- 6: Subject is not in hospital - unable to assess

H1 Recipient weight at this assessment
Pounds ☐ Not Done

H2 Serum alanine aminotransferase (ALT) at this assessment
IU/L ☐ Not Done

H3 Serum aspartate aminotransferase (AST) at this assessment
IU/L ☐ Not Done

H4 Serum alkaline phosphatase (ALK) at this assessment
IU/L ☐ Not Done

H5 Total serum bilirubin at this assessment
mg/dl ☐ Not Done

H6 Serum sodium at this assessment
MEq/L ☐ Not Done

H7 Serum creatinine at this assessment
mg/dl ☐ Not Done

H8 Total serum albumin at this assessment
g/dl ☐ Not Done

H9 INR at this assessment
INR Units ☐ Not Done

H10 Blood Urea Nitrogen (BUN) at this assessment
mg/dl ☐ Not Done

H11 Hemoglobin (Hgb) at this assessment
g/dl ☐ Not Done

H12 White blood count (WBC) at this assessment
x10^3/mm^3 ☐ Not Done

H13 Platelet count at this assessment
x10^3/mm^3 ☐ Not Done

H14 Did the patient have a drain in place at this assessment?

- --
- 1: Yes
- 2: No

Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.

Drain output at this assessment
L/24 hrs ☐ Not Done

H15 Degree of hepatic encephalopathy:

Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.

- --
- 0: None
- 1: Subject intubated/sedated - unable to assess
- 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior.
- 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation.

	○ 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli). ○ 6: Subject is not in hospital - unable to assess	
I1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ○ -- ○ 1: Yes ○ 2: No	

eCRF revised 06102013
Annotation revised 07222013

Print

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Tasks

Post-Txp Month 1 Assessment

Site ID:	902

Subject ID : Name	R4162 : iL4dsBSO, q/EMkcDe

The visit window for Month 1 is Day 23 to Day 60.

A1 Date of contact:

Month Day Year

A2 What is the recipient's current status? (if dead, enter death information on subject page)

- --
- 1: Alive
- 2: Dead
- 998: Unknown

A3 What is the status of the liver graft? (if failed, enter retransplant date and cause of graft failure on subject page)

- --
- 1: Functional
- 2: Failed
- 3: Unknown

A4 Did the patient have a biopsy performed since the last assessment? (if yes, fill out biopsy report CRF)

This includes all "for cause" biopsies as well as those for HCV pre and post treatment.
For all biopsies performed a post-transplant biopsy report must be completed.

- --
- 1: Yes
- 2: No

A5 Has the patient been hospitalized since the last assessment? (If yes, fill out Hospitalization CRF.)

- --
- 1: Yes
- 2: No

A6 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)

- --
- 1: Yes
- 2: No

A7 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)

- --
- 1: Yes
- 2: No

A8 Recipient medical condition at this assessment.

- --
- 1: Patient in ICU
- 2: Hospitalized, not in ICU
- 3: In rehab facility
- 4: Not hospitalized

Recipient on ventilator at this assessment?

A9
- --
- 1: Yes
- 2: No
- 998: Unknown

A10
What was the immunosuppression regimen in place during this assessment? (Check all that apply)

Click to Expand/Collapse

- ☐ Prednisone (or oral equivalent)
- ☐ Methylprednisolone (or IV equivalent)
- ☐ Cyclosporine (Neoral, Gengraf or any other formulation)
- ☐ Tacrolimus (Prograf)
- ☐ Rapamycin (Sirolimus, Rapamune)
- ☐ Certican (RAD) (Everolimus)
- ☐ Azathioprine (Imuran or generic)
- ☐ Mycophenolate mofetil (Cellcept or generic)
- ☐ Enteric-coated mycophenolic (Myfortic or generic)
- ☐ Other immunosuppression (specify)

Specify "other" immunosuppression:

A11
Did the patient have a rejection episode that was confirmed by a biopsy since the last assessment?

For all biopsies performed a post-transplant biopsy report must be completed.

- --
- 1: Yes
- 2: No

If yes, how many biopsy-proven rejection episodes has the patient had since the last assessment?

A12
Recipient on dialysis at this assessment?
- --
- 1: No
- 2: Hemodialysis/CVVHD
- 3: Peritoneal Dialysis
- 4: Dialysis - Unknown Type
- 998: Unknown

B1
Recipient weight at this assessment
Pounds ☐ Not Done

B2
Serum alanine aminotransferase (ALT) at this assessment
IU/L ☐ Not Done

B3
Serum aspartate aminotransferase (AST) at this assessment
IU/L ☐ Not Done

B4
Serum alkaline phosphatase (ALK) at this assessment
IU/L ☐ Not Done

B5
Total serum bilirubin at this assessment
mg/dl ☐ Not Done

B6
Serum sodium at this assessment
MEq/L ☐ Not Done

B7
Serum creatinine at this assessment
mg/dl ☐ Not Done

B8
Total serum albumin at this assessment
g/dl ☐ Not Done

B9
INR at this assessment
INR Units ☐ Not Done

B10	Blood Urea Nitrogen (BUN) at this assessment mg/dl ☐ Not Done	
B11	Hemoglobin (Hgb) at this assessment g/dl ☐ Not Done	
B12	White blood count (WBC) at this assessment x10^3/mm^3 ☐ Not Done	
B13	Platelet count at this assessment x10^3/mm^3 ☐ Not Done	
B14	Did the patient have a drain in place at this assessment? ○ -- ○ 1: Yes ○ 2: No Only measure the abdominal drain outputs, biliary drains or stent outputs are not to be included in the measured outputs. Source documents should clearly show the daily measured amounts.	
	Drain output at this assessment L/24 hrs ☐ Not Done	
B15	Degree of hepatic encephalopathy: ○ -- ○ 0: None ○ 1: Subject intubated/sedated - unable to assess ○ 2: Grade 1 - Trivial lack of awareness; Euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction ○ 3: Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior. ○ 4: Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation. ○ 5: Grade 4 - Coma (unresponsive to verbal or noxious stimuli). ○ 6: Subject is not in hospital - unable to assess Daily grading of encephalopathy must be clearly sourced. The DCC provides a source document tool for your use.	
C1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ○ -- ○ 1: Yes ○ 2: No	

eCRF revised 06102013
Annotation revised 07222013

Print

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Tasks

Post-Txp Month 3 Assessment

Site ID:	902

Subject ID : Name	R4162 : iL4dsBSO, q/EMkcDe

The visit window for Month 3 is Day 61 to Day 228.

A1 Date of contact:

Month Day Year

A2 What is the recipient's current status? (if dead, enter death information on subject page)

- --
- 1: Alive
- 2: Dead
- 998: Unknown

A3 What is the status of the liver graft? (if failed, enter retransplant date and cause of graft failure on subject page)

- --
- 1: Functional
- 2: Failed
- 3: Unknown

A4 Did the patient have a biopsy performed since the last assessment? (if yes, fill out biopsy report CRF)

- --
- 1: Yes
- 2: No

This includes all "for cause" biopsies as well as those for HCV pre and post treatment.
For all biopsies performed a post-transplant biopsy report must be completed.

A5 Has the patient been hospitalized since the last assessment? (If yes, fill out Hospitalization CRF.)

- --
- 1: Yes
- 2: No

A6 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)

- --
- 1: Yes
- 2: No

A7 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)

- --
- 1: Yes
- 2: No

A8 Recipient medical condition at this assessment.

- --
- 1: Patient in ICU
- 2: Hospitalized, not in ICU
- 3: In rehab facility
- 4: Not hospitalized

Recipient on ventilator at this assessment?

A9

- --
- 1: Yes
- 2: No
- 998: Unknown

A10

What was the immunosuppression regimen in place during this assessment? (Check all that apply)

Click to Expand/Collapse

- ☐ Prednisone (or oral equivalent)
- ☐ Methylprednisolone (or IV equivalent)
- ☐ Cyclosporine (Neoral, Gengraf or any other formulation)
- ☐ Tacrolimus (Prograf)
- ☐ Rapamycin (Sirolimus, Rapamune)
- ☐ Certican (RAD) (Everolimus)
- ☐ Azathioprine (Imuran or generic)
- ☐ Mycophenolate mofetil (Cellcept or generic)
- ☐ Enteric-coated mycophenolic (Myfortic or generic)
- ☐ Other immunosuppression (specify)

Specify "other" immunosuppression:

A11

Did the patient have a rejection episode that was confirmed by a biopsy since the last assessment?

For each biopsy performed a post-transplant biopsy report must be completed.

- --
- 1: Yes
- 2: No

If yes, how many biopsy-proven rejection episodes has the patient had since the last assessment?

A12

Recipient on dialysis at this assessment?

- --
- 1: No
- 2: Hemodialysis/CVVHD
- 3: Peritoneal Dialysis
- 4: Dialysis - Unknown Type
- 998: Unknown

B1

Recipient weight at this assessment

Pounds ☐ Not Done

B2

Serum alanine aminotransferase (ALT) at this assessment

IU/L ☐ Not Done

B3

Serum aspartate aminotransferase (AST) at this assessment

IU/L ☐ Not Done

B4

Serum alkaline phosphatase (ALK) at this assessment

IU/L ☐ Not Done

B5

Total serum bilirubin at this assessment

mg/dl ☐ Not Done

B6

Serum creatinine at this assessment

mg/dl ☐ Not Done

B7

Total serum albumin at this assessment

g/dl ☐ Not Done

B8

INR at this assessment

INR Units ☐ Not Done

B9

Hemoglobin (Hgb) at this assessment

g/dl ☐ Not Done

B10	White blood count (WBC) at this assessment x10^3/mm^3 ☐ Not Done	
B11	Platelet count at this assessment x10^3/mm^3 ☐ Not Done	
C1	Liver volume (CT or MR): cc	
C2	Spleen Volume (CT or MR): cc	
D1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ○ -- ○ 1: Yes ○ 2: No	

eCRF revised 06102013
Annotation revised 07222013

Print

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Tasks

Post-Txp Year Assessment

Site ID:	902

Subject ID : Name	R4162 : iL4dsBSO, q/EMkcDe

A1 Date of contact: ____ ____ ____ (Month Day Year)

The visit windows for yearly assessments are +or- 6 months from Yearly visit Date

A2 What is the recipient's current status? (if dead, enter death information on subject page)
- --
- 1: Alive
- 2: Dead
- 998: Unknown

A3 What is the status of the liver graft? (if failed, enter retransplant date and cause of graft failure on subject page)
- --
- 1: Functional
- 2: Failed
- 3: Unknown

A4 Did the patient have a biopsy performed since the last assessment? (if yes, fill out biopsy report CRF)
- --
- 1: Yes
- 2: No

This includes all "for cause" biopsies as well as those for HCV pre and post treatment.
For all biopsies performed a post-transplant biopsy report must be completed.

A5 Has the patient been hospitalized since the last assessment? (If yes, fill out Hospitalization CRF.)
- --
- 1: Yes
- 2: No

A6 Has the patient experienced a study-tracked complication since the last assessment? (If yes, fill out Complication CRF.)
- --
- 1: Yes
- 2: No

A7 Has the patient experienced an SAE since the last assessment? (If yes, fill out SAE CRF.)
- --
- 1: Yes
- 2: No

A8 Recipient medical condition at this assessment.
- --
- 1: Patient in ICU
- 2: Hospitalized, not in ICU
- 3: In rehab facility
- 4: Not hospitalized

Recipient on ventilator at this assessment?

A9

- --
- 1: Yes
- 2: No
- 998: Unknown

A10

What was the immunosuppression regimen in place during this assessment? (Check all that apply)

Click to Expand/Collapse

- Prednisone (or oral equivalent)
- Methylprednisolone (or IV equivalent)
- Cyclosporine (Neoral, Gengraf or any other formulation)
- Tacrolimus (Prograf)
- Rapamycin (Sirolimus, Rapamune)
- Certican (RAD) (Everolimus)
- Azathioprine (Imuran or generic)
- Mycophenolate mofetil (Cellcept or generic)
- Enteric-coated mycophenolic (Myfortic or generic)
- Other immunosuppression (specify)

Specify "other" immunosuppression:

A11

Did the patient have a rejection episode that was confirmed by a biopsy since the last assessment?

For all biopsies performed a post-transplant biopsy report must be completed.

- --
- 1: Yes
- 2: No

If yes, how many biopsy-proven rejection episodes has the patient had since the last assessment?

A12

Recipient on dialysis at this assessment?

- --
- 1: No
- 2: Hemodialysis/CVVHD
- 3: Peritoneal Dialysis
- 4: Dialysis - Unknown Type
- 998: Unknown

B1

Recipient weight at this assessment

Pounds Not Done

B2

Serum alanine aminotransferase (ALT) at this assessment

IU/L Not Done

B3

Serum aspartate aminotransferase (AST) at this assessment

IU/L Not Done

B4

Serum alkaline phosphatase (ALK) at this assessment

IU/L Not Done

B5

Total serum bilirubin at this assessment

mg/dl Not Done

B6

Serum creatinine at this assessment

mg/dl Not Done

B7

Total serum albumin at this assessment

g/dl Not Done

B8

INR at this assessment

INR Units Not Done

B9

Hemoglobin (Hgb) at this assessment

g/dl Not Done

B10	White blood count (WBC) at this assessment x10^3/mm^3 Not Done	
B11	Platelet count at this assessment x10^3/mm^3 Not Done	
C1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): -- 1: Yes 2: No	

eCRF revised 06102013
Annotation revised 07222013

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Tasks

Recipient Complications

Site ID:	901
Subject ID : Name	R5273 : xZHt/O88, 9HqtH1vf

Please refer to the MOO for the list of complications being tracked as part of the study. The drop down list here contains those complications.

A1	ComplicationType: --	
A2	Date of onset: Month Day Year	The onset date is the first date the complication is mentioned in the source documents. If the onset date is reported by the subject during a clinic visit, the information should be reported in the subject's chart.
A3	Ongoing? -- / 1: Yes / 2: No	The resolution date is the date the complication is no longer mentioned in the source documents. If the resolution date is reported by the subject during a clinic visit, the information should be reported in the subject's chart. If a subject dies and a complication date can not be located in the chart, the date of death should be entered.
A4	Date of resolution: Month Day Year	

A2ALL Adult To Adult Living Donor Liver Transplantation Study

A2ALL-link Secure Site (Production)

Site Name: Columbia (310) | Home | Tasks | Subject List | Shipping | Announcements | My Account | Online Help | Contact Us | Reports | Logout | Patient Name Key

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Hospitalization

Site ID:	310
Subject ID : Name	R1257 : LpY/WwAN, +EsEpN5j

Admissions less than 24 hours are not considered hospitalizations and should not be reported as such.

A1 Date of Admission:
Month Day Year

A2 Date of Discharge:
Month Day Year

If recipient is re-transplanted during initial transplant hospital admission, use the date of re-transplant as the date of discharge and enter a comment that the subject was still hospitalized for re-txp.

A3 Was this admission associated with a study-tracked post-transplant complication? (If yes, fill out Complication CRF.)
- --
- 1: Yes
- 2: No

Refer to the MOO for the list of those complications being tracked by this study.

A4 Discharge Destination:
- --
- 1: Home
- 2: Hospital-affiliated transitional residence
- 3: Transfer to another hospital
- 4: Rehabilitation facility
- 5: Nursing home
- 6: Other
- 7: N/A (patient died)

A5 Number of days in ICU (enter "0" for none, leave blank if unknown):

If a subject spends overnight in the PACU this is considered 1day in the ICU. If a subject spends overnight in the PACU and one day in the ICU this is considered 2 days in the ICU

A6 Type of hospital:
- --
- 1: A2ALL hospital
- 2: Non-A2ALL hospital

A7 Type of hospital admission:
--

The ICD 9 code used here is the primary reason for the hospital admission. For the transplant admission use the ICD 9 code of the reason for transplant.

A8 Discharge diagnosis (enter discharge numeric ICD-9/10 diagnosis code):

More than one ICD 9 code can be entered, they must be seperated by a comma.

Print

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Tasks

Protocol Deviations

Site ID:	902
Subject ID : Name	R4614 : 5aVOttwz, Ppkx9Qw9

Complete questions A1 through A8 and save, then print the form. Have the PI review the deviation and have them complete questions A9 and A10. Fax the completed and signed form to the DCC (734) 665-2103. The Project Manager at the DCC will review the form and sign. It will be scanned and returned to the site electronically.
Please refer to the MOO for examples of various deviations.
All deviations should be submitted to your IRB, per their reporting procedures. The response to the deviation reports should be filed in the regulatory binder under major correspondence.

A1 Date Deviation Occurred
Month Day Year

A2 Date DCC Notified
Month Day Year

A3 Protocol Deviation
- (•) --
- ( ) 1: Subject enrolled, but does not meet eligibility criteria.
- ( ) 2: Non-adherence to study design.
- ( ) 3: Loss of samples or data as per protocol schedule of events.
- ( ) 4: Failure to obtain informed consent prior to initiation of study-related procedures.
- ( ) 5: Falsifying research or medical records.
- ( ) 6: Performing tests beyond professional scope.
- ( ) 7: Working under an expired professional license or certification.
- ( ) 8: Breach of confidentiality.
- ( ) 9: Improper or inadequate informed consent procedure.
- ( ) 10: Other, specify

Specify "other" protocol deviation:

A4 Protocol Deviation Description

A5 Protocol Version
- (•) --
- ( ) 1: Original Protocol
- ( ) 2: Amendment Number

If amendment, specify version:

A6 Steps taken to resolve this deviation

A7 Completed by:

A8 Date of Completion:
Month Day Year

A9	Date Principal Investigator (PI) Reviewed Form: Month Day Year	
A10	PI signature:_____ Date:___/___/_____	
	The following questions are for DCC use only	
A11	Is this a major or minor protocol deviation? (•) -- ( ) 1: Major ( ) 2: Minor	
A12	DCC Monitor Review	
A13	DCC Project Manager Signature_____ Date:___/___/_____	

A2ALL Adult To Adult Living Donor Liver Transplantation Study

A2ALL-link Secure Site (Production)

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

Serious Adverse Event (SAE)

Site ID:	310

Subject ID : Name	R1257 : LpY/WwAN, +EsEpN5j

Only report Serious Adverse Events related to the protocol mandated procedures: Phlebotomy, Survey Response, Height/Weight Measurement, MRI/CT, Liver Biopsy, Pressure and Flow Measurements. To be considered a Serious Adverse Event, one or more of the following must apply: Death, Life threatening, Persistent or significant disability/incapacity, Required in-patient hospitalization or prolonged hospitalization, congenital anomaly or birth defect, Important medical events requiring medical or surgical intervention to prevent one of the outcomes listed above.

A1 Date of this report: [ ] [ ] [ ] Today
Month Day Year

A2 Start Date of Event: [ ] [ ] [ ]
Month Day Year

The SAE' must be reported to the DCC within 24 Hrs of the site's awareness of the occurrence. The site should complete the SAE report in A2ALL-Link within this time frame. Once the form is saved, and email notification will be sent to the DCC and the NIDDK.

A3 End Date of Event: [ ] [ ] [ ]
Month Day Year

A4 ICD-9/10 Code: [ ]

Enter the ICD 9 Code related to the SAE

A5 Severity of event (assessed by PI):
- (•) --
- ( ) 1: Mild
- ( ) 2: Moderate
- ( ) 3: Severe

The PI assessment of severity, will need to be documented on a source document

A6 Pattern of event:
- (•) --
- ( ) 1: Single episode
- ( ) 2: Intermittent
- ( ) 3: Continuous

A7 Relatedness of event to study procedure (assessed by PI) (if unrelated go to question A8):
- (•) --
- ( ) 1: Unrelated
- ( ) 2: Remote
- ( ) 3: Possible
- ( ) 4: Probable
- ( ) 5: Related

(If related, possibly related, probably related, or remotely related), which study procedure?
- (•) --
- ( ) 1: Liver biopsy
- ( ) 2: Phlebotomy
- ( ) 3: MRI, CT, or other imaging study
- ( ) 4: QOL assessment
- ( ) 5: Pressure or flow measurement

Action(s) taken (check all that apply)

A8

Click to Expand/Collapse

- ☐ None
- ☐ Additional meds
- ☐ Additional therapy
- ☐ Additional lab tests
- ☐ Hospitalization required
- ☐ Prolonged hospitalization required

9

SAE condition, check all that apply:

Click to Expand/Collapse

- ☐ Death
- ☐ Life-threatening
- ☐ Inpatient/prolonged hospitalization
- ☐ Congenital anomaly or birth defect
- ☐ Persistent/significant disability or incapacity
- ☐ Medically important condition

Is this an expected SAE?

- ⊙ --
- ○ 1: Yes
- ○ 2: No

A10

Has the principal investigator reviewed this report?

- ⊙ --
- ○ 1: Yes
- ○ 2: No

Date of PI review:

☐☐☐☐

Month Day Year

Print

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Tasks

HCV Study Subject Flow

Site ID:	901
Subject ID : Name	R4914 : kVPSi+uf, 9HqtH1vf

The HCV Study Subject Flow eCRF will be the first eCRF to populate, once an HCV subject reaches 3 years (or more) post txp. The answers here will populate additional eCRFs if the subject is eligible for the study. If the subject does not meet inclusion criteria for the study, the subject's consent status should be changed to "subject entered by mistake".

A1 Did the recipient receive any pre-transplant HCV treatment?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

If yes, did the recipient achieve SVR (non-detectable HCV RNA at least six months after end of treatment)?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

This question refers to pre-transplant treatment. If the subject was still on treatment prior to transplant and did not achieve SVR pre-transplant, answer no to this question. Subject is not eligible for the study if the answer is yes.

If yes, date of SVR:

[ ][ ][ ]
Month Day Year

A2 Was the recipient co-infected with hepatitis B virus (HBsAg-positive) or with HIV before transplant?
- (•) --
- ( ) 1: Yes
- (•) 2: No

Subject is ineligible if the answer is yes.

A3 Did the recipient receive a graft from an HCV-infected donor?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

Subject is ineligible if the answer is yes.

A4 Was the recipient one of the first 20 LDLT recipients at this transplant center?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

Subject is ineligible if the answer is yes.

A5 Was the recipient retransplanted less than 90 days after receiving the index transplant?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

Subject is ineligible if the answer is yes.

A6 Did the recipient die less than 90 days after transplant?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

Subject is ineligible if the answer is yes.

B1 Is subject alive with index graft?
- (•) --
- ( ) 1: Yes
- ( ) 2: No

The index graft refers to the first liver graft that was transplanted.

Does subject have evidence of cirrhosis?

B2 Cirrhosis is defined by Ishak fibrosis stage > or = to 5 based on histology, or liver stiffness >12.5 kPa by transient elastography, and/or advanced HCV disease based on clinical criteria (in patients who do not undergo liver biopsy or transient elastography).

-- / 1: Yes / 2: No

If yes, source of evidence indicating cirrhosis (if Biopsy findings checked, please fill out a biopsy report CRF)

-- / Biopsy findings / Clinical evidence

If yes to Biopsy findings, complete a biopsy report eCRF and contact the pathology dept. where Bx was obtained to inquire about obtaining 4 slides (trichrome, H&E, and 2 unstained) for Central Read. The biopsy first showing cirrhosis (select HCV Protocol on Bx eCRF) and the first biopsy prior to that not showing cirrhosis will be needed for central read.

B3 Has the subject had a biopsy within the past 12 months? (if yes, please fill out a biopsy report CRF)

-- / 1: Yes / 2: No

If subject has a biopsy scheduled in the next three months, enter the date of the biopsy in the comment box and answer "no" to this question. If the subject had a Bx in the past 12 months and doesn't have another biopsy scheduled (in next 3 months) answer yes, complete a biopsy report eCRF and contact the pathology dept. where Bx was obtained to inquire about obtaining 4 slides (trichrome, H&E, and 2 unstained) for Central read.

B4 Will the subject undergo the ≥ 3 year protocol biopsy? (If yes, please fill out a biopsy report CRF)

-- / 1: Yes / 2: No

If yes,collect 4 Bx slides for Central Read, and obtain Biosamples at visit, as well as completing the biopsy report eCRF. If no, contact the pathology department and obtain the most recent biopsy collected and obtain the 4 slides for central read

If no, reason for not performing liver biopsy

-- / Subject did not consent / Coagulopathy or thrombocytopenia precluding safe biopsy / Other condition precluding safe biopsy / Achieved SVR after post-LT HCV treatment

If the PI does not recommend a biopsy for this subject due to age or other clinical concerns not included in the categories below, please select "Subject Did Not Consent" and add a comment in the comment box.

B5 Is transient elastography available for this patient?

-- / 1: Yes / 2: No

Transient Elastography / Fibroscan is currently available at NWU, UCSF, and Toronto. If yes, complete HCV Transient Elastography eCRF.

B6 Has the subject been retransplanted?

-- / 1: Yes / 2: No

If yes, do not obtain any previous biopsy slides for central read

If yes, date of retransplant:

Month Day Year

B7 Did the subject die? (If yes, please enter date on subject information screen.)

-- / 1: Yes / 2: No

If yes, do not obtain any previous biopsy slides for central read

C1 Questionnaire Completed

Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.

This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC):

-- / 1: Yes / 2: No

eCRF revised 05032013

Annotation revised 07222013

A2ALL-link Secure Site (Test)

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

HCV Transient Elastography Report

Site ID:	902

Subject ID : Name	R4613 : Vee, HC

NWU, UCSF, and Toronto are the only sites that will be utilizing this eCRF.
If your site is not listed above, please contact the DCC.

A1 Liver stiffness measurement [ ] [--] ☐ Not Done

A2 Date of transient elastography:
[ ] [ ] [ ]
Month Day Year

B1 Questionnaire Completed

Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.

This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC):
- ◉ --
- ○ 1: Yes
- ○ 2: No

A2ALL Adult To Adult Living Donor Liver Transplantation Study

A2ALL-link Secure Site (Production)

Site Name: Test901 (901) | Home | Tasks | Subject List | Shipping | Announcements | My Account | Online Help | Contact Us | Reports | Logout | Patient Name Key

Print

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Tasks

Post-TXP BX Results

Site ID:	901
Subject ID : Name	R4914 : kVPSi+uf, 9HqtH1vf

Reminder:for all "HCV only" subjects (dead or alive). All previous post-txp biopsies should be reviewed and recorded on a Post-Txp Biopsy eCRF in A2ALL-link.
Continuing Sites should review previously recorded biopsies in BioDBx, for subjects previously enrolled in the Cohort Study. Only complete A2ALL-link post-txp biopsy eCRF for those not previously recorded in BioDBx or A2ALLlink (if a CORE enrolled subject).

A1 Date of Biopsy:
Month Day Year

A2 Reason(s) for Biopsy (check all that apply)
- ☐ R/O HCV Recurrence
- ☐ R/O Rejection
- ☐ Abnormal LFTs
- ☐ Routine
- ☐ HCV Protocol

Check all that apply (example, if a biopsy was done to r/o rejection, and it falls within the acceptance of an HCV subject's 3 (+) year biopsy (within last 12 months), check R/o Rejection and HCV Protocol). The HCV Protocol box must be checked if answered "yes" to question B3 or B4 (new biopsy collected or biopsy within past 12 months) on HCV Subject Flow eCRF.

A3 For HCV protocol biopsies, what was the route of the biopsy?
- ⊙ --
- ○ 1: Transabdominal
- ○ 2: Transjugular

If transjugular, hepatic venous pressure gradient:
1: mmHg ☐ Not Done

A4 Diagnosis (check all that apply) (if HCV, indicate Ishak stage below, if rejection, indicate severity below)
- ☐ HCV
- ☐ Rejection - Acute
- ☐ Rejection - Chronic
- ☐ CMV Hepatitis
- ☐ Acute Hepatitis Not Specified
- ☐ Chronic Hepatitis Not Specified
- ☐ Ischemic Hepatitis
- ☐ Biliary Obstruction
- ☐ Cholestasis Not Specified
- ☐ NASH/NAFLD
- ☐ Normal
- ☐ Other

Specify "other" diagnosis:

If HCV, indicate the fibrosis stage
- ⊙ --
- ○ Ishak stage 0 – No Fibrosis
- ○ Ishak stage 1 – Fibrosis expansion of some portal areas, with or without short fibrous septa
- ○ Ishak stage 2 – Fibrous expansion of most portal areas, with or without short fibrous septa
- ○ Ishak stage 3 – Fibrous expansion of most portal areas with occasional portal to portal (p-p) bridging

- ○ Ishak stage 4 – Fibrous expansion of portal areas, with marked bridging (p-p) as well as portal to central (p-c)
- ○ Ishak stage 5 – Marked bridging (p-p and/or p-c) with occasional nodules (incomplete cirrhosis)
- ○ Ishak stage 6 – Cirrhosis; probable or definite
- ○ No cirrhosis – As determined by alternative scoring system (e.g., METAVIR, Ludwig, Knodell or Scheuer <4) or specific notation on the biopsy path report that there is no cirrhosis
- ○ Cirrhosis – As determined by alternative scoring system (e.g., METAVIR, Ludwig, Knodell or Scheuer =4) or specific notation on the biopsy path report that cirrhosis is present
- ○ Not available

If Rejection, what was the severity?

- ◉ --
- ○ 1: Mild
- ○ 2: Moderate
- ○ 3: Severe
- ○ 4: Not noted

eCRF revised 05062013
Annotation revised 07222013

Print

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Tasks

HCV Transplant Information

Site ID:	901
Subject ID : Name	R4914 : kVPSi+uf, 9HqtH1vf

Please have source documentation for all the following data available in the study subject's research chart.

A1 Recipient height _____ Inches

A2 Recipient weight at transplant _____ Pounds

A3 Did the recipient have a diagnosis of HCC before transplant?
- --
- 1: Yes
- 2: No

A4 Was the recipient on dialysis at the time of transplant?
- --
- 1: Yes
- 2: No

B1 UNOS Donor ID _____

B2 Donor age _____ years

B3 Donor gender
- --
- 1: Male
- 2: Female

B4 Donor Ethnicity
- --
- 1: Hispanic/Latino
- 2: Non-Hispanic/Non-Latino
- 9: Unknown

B5 Donor Race
- --
- 1: America Indian or Alaskan Native
- 2: Asian (includes Indian, subcontinent)
- 3: Black or African American
- 4: Native Hawaiian or Other Pacific Islander
- 5: White (includes Middle Eastern)
- 6: Multi-Racial, not specified
- 9: Unknown

Donor type
- --

B6
- 1: DDLT
- 2: LDLT

B7 If DDLT, what was the donor's cause of death?
- --
- 1: Anoxia
- 2: Cerebrovascular/stroke
- 3: Head trauma
- 4: CNS Tumor
- 999: Other

B8 If DDLT, was this a DCD (Donation after Cardiac Death) donor?
- --
- 1: Yes
- 2: No

B9 If DDLT, what was the graft type?
- --
- 1: Whole liver
- 2: Split liver

B10 if LDLT, what was the graft type?
- --
- 1: Right lobe
- 2: Left lobe
- 3: Left lateral segment

B11 Warm ischemia time _____ minutes

B12 Cold ischemia time _____ minutes

C1 HCV Genotype
- --
- 1: 1, subtype unspecified or mixed
- 2: 1, a
- 3: 1, b
- 4: 2
- 5: 3
- 6: 4
- 7: 5
- 8: 6
- 9: Other, specify
- 998: Unknown

Specify "other" HCV genotype: _____

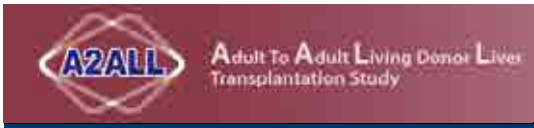
C2 Was the patient's HCV RNA closest to transplant detectable?
- --
- 1: Yes
- 2: No
- 998: Unknown

Date of HCV RNA: ___ ___ _____
Month Day Year

Serum alanine aminotransferase (ALT) closest to the time of transplant

C3	IU/L ☐ Not Done	
C4	Serum aspartate aminotransferase (AST) closest to the time of transplant IU/L ☐ Not Done	
C5	Serum alkaline phosphatase (ALK) closest to the time of transplant IU/L ☐ Not Done	
C6	Total bilirubin closest to the time of transplant mg/dl ☐ Not Done	
C7	Serum creatinine closest to the time of transplant mg/dl ☐ Not Done	
C8	Albumin closest to the time of transplant g/dl ☐ Not Done	
C9	INR closest to the time of transplant INR Units ☐ Not Done	
D1	What was the immunosuppression regimen in place one year post-transplant? (Check all that apply) Click to Expand/Collapse ☐ Prednisone (or oral equivalent) ☐ Methylprednisolone (or IV equivalent) ☐ Cyclosporine (Neoral, Gengraf or any other formulation) ☐ Tacrolimus (Prograf) ☐ Rapamycin ☐ Certican (RAD) ☐ Azathioprine (Imuran or generic) ☐ Mycophenolate mofetil (Cellcept or generic) ☐ Enteric-coated mycophenolic (Myfortic or generic) ☐ Other immunosuppression (specify)	
	Specify "other" immunosuppression:	
E1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ○ -- ○ 1: Yes ○ 2: No	

eCRF revised 07152013
Annotation revised 07222013



A2ALL-link Secure Site (Production)

Print

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Tasks

HCV Study Information

Site ID:	901
Subject ID : Name	R4914 : kVPSi+uf, 9HqtH1vf

Date of cirrhosis assessment should be:
1. Protocol Bx Date if applicable
2. If previous Bx with documented cirrhosis, date of biopsy
3. If Alive w/o Re-txp, Date of completion of Advanced Disease eCRF
4. If Alive w/Re-txp, Date of re-txp
5. If Dead w/o Re-Txp, enter date of death
6. If Dead w/ Re-Txp, enter date of Re-Txp.

A1 Date of cirrhosis assessment
Month Day Year

Completion of all the questions on this form will be for the time point: "From the date of transplant(index graft)to the date of Cirrhosis assessment". (Date of Cirrhosis Assessment is identified in #1-#6 above).

A2 Did the patient receive HCV treatment post-LT?
- --
- 1: Yes
- 2: No

Thorough review of the subject's medical chart is needed to complete the next data elements regarding HCV treatment post-transplant.

If yes, how many courses of HCV treatment did the patient receive?
- --
- 1: 1 only
- 2: >1

If the subject had a treatment regimen that was immediately followed by a maintenance treatment, consider this one treatment. If subject is on a maintenance dose of interferon post txp, include this as a course of treatment, leave the end date blank and add a comment in the comment box stating the treatment is ongoing at this time.

Start date of most recent course of treatment
Month Day Year

End date of most recent course of treatment
Month Day Year

Drugs used for most recent treatment (check all that apply)
- PegInterferon
- Ribavirin
- Direct acting antiviral (DAA)
- Other (specify)

Specify "other" drug

If treated, did the patient achieve SVR (undetectable HCV RNA 6 months after stopping treatment)?
- --
- 1: Yes
- 2: No
- 998: Unknown

Source documentation will need to be provided showing the end date of treatment and the undetectable HCV RNA 6 months after the end of treatment.

If yes, date of HCV RNA confirming SVR:
Month Day Year

A3 Was the patient ever treated for rejection with pulsed steroids and/or antibodies?
- --
- 1: Yes

Source will need to be provided for data entered for these questions.

2: No

If yes, how many times?

--

1: 1

2: >1

Start date of first rejection treatment:

Month Day Year

A4 Was the patient ever treated for post-transplant CMV viremia?

--

1: Yes

2: No

CMV viremia is defined as positive CMV by PCR.
Source documents will need to be provided for data entered for this question.

If yes, date of initial CMV viremia treatment:

Month Day Year

A5 Did the patient develop any biliary complications?

--

1: Yes

2: No

If this is an active Core subject each biliary complication should also be reported as study tracked complication and a complication eCRF should be completed for each complication.
Remember the time frame is from the index graft to the time of Cirrhosis Assessment (A1).

If yes, initial biliary complication type

--

1: Biliary leak

2: Biliary stricture

3: Simultaneous leak and stricture

If yes, date of initial biliary complication

Month Day Year

B1 Weight closest to the time of cirrhosis assessment

Pounds

Cirrhosis Assessment is the date entered in A1 above.

B2 Treated diabetes present at the time of cirrhosis assessment?

--

1: Yes

2: No

998: Unknown

The time of Cirrhosis Assessment is defined as the date entered in A1 above.

Source document will need to be provided for data entered for this question.

B3 What was the immunosuppression regimen in place at the time of cirrhosis assessment? (Check all that apply)

Click to Expand/Collapse

- Prednisone (or oral equivalent)
- Methylprednisolone (or IV equivalent)
- Cyclosporine (Neoral, Gengraf or any other formulation)
- Tacrolimus (Prograf) (FK506)
- Rapamycin (Sirolimus or Rapamune)
- Certican (RAD) (Everolimus)
- Azathioprine (Imuran or generic)
- Mycophenolate mofetil (Cellcept or generic)
- Enteric-coated mycophenolic (Myfortic or generic)
- Other immunosuppression (specify)

Specify "other" immunosuppression:

Was the patient's HCV RNA closest to cirrhosis assessment detectable?

--

C1	○ 1: Yes ○ 2: No ○ 998: Unknown	
	Date of HCV RNA closest to cirrhosis assessment Month Day Year Cirrhosis Assessment is the date entered in A1 above.	
C2	Serum alanine aminotransferase (ALT) closest to cirrhosis assessment IU/L ☐ Not Done	
C3	Serum aspartate aminotransferase (AST) closest to cirrhosis assessment IU/L ☐ Not Done	
C4	Serum alkaline phosphatase (ALK) closest to cirrhosis assessment IU/L ☐ Not Done	
C5	Total bilirubin closest to cirrhosis assessment mg/dl ☐ Not Done	
C6	Serum creatinine closest to cirrhosis assessment mg/dl ☐ Not Done	
C7	Albumin closest to cirrhosis assessment g/dl ☐ Not Done	
C8	INR closest to cirrhosis assessment INR Units ☐ Not Done	
C9	Hemoglobin (Hgb) closest to cirrhosis assessment g/dl ☐ Not Done	
C10	White blood count (WBC) closest to cirrhosis assessment x10^3/mm^3 ☐ Not Done	
C11	Platelet count closest cirrhosis assessment x10^3/mm^3 ☐ Not Done	
D1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ○ -- ○ 1: Yes ○ 2: No	

eCRF revised 07152013
Annotation revised 07222013

Print

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Tasks

HCV Advanced Disease Assessment

Site ID:	901

Subject ID : Name	R4914 : kVPSi+uf, 9HqtH1vf

A1 Date of advanced disease assessment

Month Day Year

The date entered is the date this eCRF is completed. This eCRF is completed to document the signs, symptoms and laboratory values that point to advanced disease, and the dates they occurred. The time frame is from transplant to re-transplant or death.

A2 Is liver histology available from an explant (if retransplanted) or autopsy (if patient died)?

- --
- 1: Yes
- 2: No

If yes, please enter the date of the explant or autopsy. Please provide a copy of de-identified (labeled with A2ALL ID) explant path or autopsy report.

Month Day Year

The site should hold onto this source in the subject's study records. The DCC will ask for these reports at a future date. Explant from the index graft (subject re-transplanted)or autopsy (subject's death after index graft transplanted).

Fibrosis scoring method on biopsy from explant/autopsy:

- --
- 1: Ishak
- 2: Knodell
- 3: Ludwig-Batts
- 4: Metavir
- 5: Scheuer
- 98: Unknown scoring system
- 99: Not Done

If you're unable to interpret the pathology report to complete the next set of data elements ask your principal investigator for assistance. If necessary provide source document of discussion reached if not clearly shown on pathology report.

Fibrosis score on biopsy from explant/autopsy: (Ishak)

--

Fibrosis score on biopsy from explant/autopsy: (Knodell,Ludwig-Batts,Metavir,Scheuer)

--

Cholestatic hepatitis present?

- --
- 1: Yes
- 2: No

Review of the pathology report is necessary for completion of this data element, if necessary ask your principal investigator for assistance.

Clinical Complications of Portal Hypertension (Note: all non-liver causes such as vascular or renal are to be excluded)

A3 Ascites requiring diuretics occurring ≥ 6 months post-LT (note: if ascites developed earlier than 6 months but persisted to or beyond 6 months, use date of initial onset as "date of onset")

- --
- 1: Yes
- 2: No

Complete review of the subject's medical chart is needed to complete this data element.

If yes, ascites onset date:

Month Day Year

A4 Encephalopathy requiring treatment occurring ≥ 6 months post-LT (note: if encephalopathy developed earlier than 6 months but persisted to and beyond 6 months, use date of initial onset as "date of onset")
-- 1: Yes 2: No

Complete review of the subject's medical chart is needed to complete this data element.

If yes, encephalopathy onset date:
Month Day Year

A5 Varices grade ≥ 2 documented on EGD, present ≥ 6 months post-LT
-- 1: Yes 2: No

Complete review of the subject's medical chart is needed to complete this data element.

If yes, varices onset date:
Month Day Year

Persistent laboratory evidence of liver dysfunction (persistent is defined as: ≥ 2 measurements at least 4 weeks apart) 6 months or more post-LT (Note: must exclude other explanations for lab abnormalities such as biliary strictures, nephrotic syndrome, Coumadin use, chronic rejection)

A6 Bilirubin ≥ 2 mg/dl
-- 1: Yes 2: No

Complete review of the subject's medical chart is needed to complete this data element.
Do not report elevated bilirubin if it's a result of cholangitis as this is a result of a bile duct infection and not liver dysfunction.
If you do not have 2 measurements at least 4 weeks apart, 6 months or more post-transplant, do not answer yes.

Bilirubin value 1
mg/dl

Bilirubin Date 1:
Month Day Year

Bilirubin value 2
mg/dl

Bilirubin date 2:
Month Day Year

A7 Albumin ≤ 3.5 g/dl
-- 1: Yes 2: No

If you do not have 2 measurements at least 4 weeks apart, 6 months or more post-transplant, do not answer yes.
Complete review of the subject's medical chart is needed to complete this data element.

Albumin value 1
g/dl

Albumin date 1:
Month Day Year

Albumin value 2
g/dl

Albumin date 2:
Month Day Year

A8 INR ≥ 1.7
-- 1: Yes

If you do not have 2 measurements at least 4 weeks apart, 6 months or more post-transplant, do not answer yes.
Complete review of the subject's medical chart is needed to complete this data element.

	○ 2: No	
	INR value 1	
	INR date 1: Month Day Year	
	INR value 2	
	INR date 2: Month Day Year	
A9	Other criteria used in making diagnosis of cirrhosis or advanced fibrosis	
A10	Investigator's assessment: Does this patient meet criteria for advanced liver disease due to recurrent HCV? (This is the most important question.) ○ -- ○ 1: Yes ○ 2: No This form is to be reviewed by the principal investigator. Once the review is complete, this question is answered, the date is entered as well as the name of the investigator who reviewed the form.	
	If yes, give approximate date of achieving advanced liver disease: Month Day Year	
A11	Investigator who reviewed this form:	
B1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ○ -- ○ 1: Yes ○ 2: No	

eCRF revised 07152013
Annotation revised 07222013

Print

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Tasks

HRQOL Only Donor Assessment

Site ID:	901
Subject ID : Name	D3903 : Wq+ew51U, DthxII9K

A source document in the subject's medical records should indicate this evaluation date. Sometimes labeled H&P evaluation.

A1 What was the date of this donor's pre-donation evaluation?

Month Day Year

A2 Donor state of permanent residence at the time of evaluation: --

This information should also be included in the evaluation report.

A3 Donor highest education level at time of evaluation:

- (•) --
- ( ) 1: None
- ( ) 2: Grade School (0-8)
- ( ) 3: High school (9-12)
- ( ) 4: Attended college/Technical school
- ( ) 5: Associate/Bachelor degree
- ( ) 6: Post-college Graduate degree
- ( ) 998: Unknown

This information should also be included in the evaluation report.

A4 Donor height at time of evaluation: Inches

same as above

A5 Donor weight at time of evaluation: Pounds

same as above

A6 Primary source of payment (may reflect recipient's medical coverage) at time of evaluation:

- (•) --
- ( ) 1: Medicare
- ( ) 2: Medicaid
- ( ) 3: US State/Govt Agency
- ( ) 4: Private Insurance
- ( ) 5: HMO/PPO
- ( ) 6: Self
- ( ) 7: Donation
- ( ) 8: Free Care
- ( ) 9: Dept. Veterans Affairs
- ( ) 10: Pending
- ( ) 11: Foreign Govt
- ( ) 12: Other (specify)
- ( ) 13: Canadian national health care
- ( ) 998: Unknown

same as above

Specify "other" source of primary payment:

Questions in this section are to be answered for the one year post-donation time point unless otherwise specified.

Review the subject's medical records for a clinic visit which is closest to the 1 year post donation time point. The one year time is from donation - 18 months. This assessment can include a phone conversation also.

B1 Date of the assessment closest to 1-year post-donation:
Month Day Year

Review the subject's medical records for a clinic visit which is closest to the 1 year post donation time point. The one year time is from donation - 18 months.

B2 Date of last face-to-face examination within the first year of donation:
Month Day Year

Enter the date of any recent clinic visit.

B3 Date of most recent face-to-face examination:
Month Day Year

Donor weight from 1 year post donation time point (B1).

B4 Donor weight:
Pounds

This should be available on a report or billing statement from the one year visit.

B5 Primary source of payment (may reflect recipient's medical coverage) at 1 year post donation assessment:
- ⊙ --
- ○ 1: Medicare
- ○ 2: Medicaid
- ○ 3: US State/Govt Agency
- ○ 4: Private Insurance
- ○ 5: HMO/PPO
- ○ 6: Self
- ○ 7: Donation
- ○ 8: Free Care
- ○ 9: Dept. Veterans Affairs
- ○ 10: Pending
- ○ 11: Foreign Govt
- ○ 12: Other (specify)
- ○ 13: Canadian national health care
- ○ 998: Unknown

Specify "other" source of primary payment:

A review of the donor's hospitalization records should be reviewed for the 1 year post donation time point. Enter a hospital eCRF for each 24 hr or more admission. Make sure to include the donation hospitalization.

B6 Has the patient been hospitalized in the first year since donation? (If yes, please fill out a hospitalization CRF for each hospitalization)
- ⊙ --
- ○ 1: Yes
- ○ 2: No

A review of the donor's medical records for the first year should be reviewed for any A2ALL tracked complications. An HRQOL Only Complication eCRF should be completed for each study tracked complication.

B7 Has the patient experienced a complication in the first year since donation? (If yes, please fill out a complication CRF for each study tracked complication)
- ⊙ --
- ○ 1: Yes
- ○ 2: No

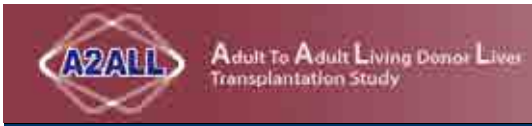
From 1 year assessment (B1) time point

B8 Donor medical condition at this assessment:
- ⊙ --
- ○ 1: Patient in ICU
- ○ 2: Hospitalized, not in ICU
- ○ 3: In rehab facility
- ○ 4: Not hospitalized

From 1 year assessment (B1) time point

Donor employment status at this assessment:
- ⊙ --
- ○ 1: Working full time
- ○ 2: Working part time by choice
- ○ 3: Working part time due to disease
- ○ 4: Working part time reason unknown

B9	○ 5: Not working by choice ○ 6: Not working due to disease ○ 7: Not working, unable to find employment ○ 8: Not working, reason unknown ○ 9: Retired ○ 998: Employment status unknown	
C1	Questionnaire Completed	
	Checking "Yes" to this question indicates that the current questionnaire or task has been completed with all available information. It will show this item as completed.	
	This Case Report Form (CRF) has been completed with all available data and should be submitted to the Data Coordinating Center (DCC): ⊙ -- ○ 1: Yes ○ 2: No	



A2ALL-link Secure Site (Production)

Print

The A2ALL Coordinating Center recommends that you print a copy of the questionnaire you just completed. Click the printer icon to view the questionnaire.

Tasks

HRQOL Only Donor Complication

Site ID:	902
Subject ID : Name	D4852 : SXTMIcSe, FhSBLXLr

A review of this HRQOL donor should be completed from the subject's medical records from the time of donation up to 15 months post donation. The drop down list in A1 includes all complications being tracked by the A2ALL2 study. Enter one complication eCRF for each complication occurring during this period.

A1 Complication type: --

Specify other infection location:

A2 Date of onset: Month Day Year

Date of first mention of this complication in the subject's medical records.

A3 Was the patient hospitalized for treatment of this complication?
-- / 1: Yes / 2: No

This should be available from the medical records.

If yes, date of hospital admission: Month Day Year

same as above

A4 Has the complication been resolved?
-- / 1: Yes / 2: No

This should be available from the medical record review.

If yes, date of resolution: Month Day Year

same as above

A5 Was it necessary to treat the complication with medications (other than immunosuppressive agents, analgesics, antipyretic, anti-inflammatory and antiemetic, drugs required for urinary retention or lower urinary tract infection, arterial hypertension, hyperlipidemia or transient hyperglycemia)?
-- / 1: Yes / 2: No

A6 Did the complication require a procedure or intervention?
-- / 1: Yes / 2: No

Type of intervention or procedure includes: Bedside therapeautic (e.g. evacuation of pneumothorax, pleural effusion or monitoring lines), surgical intervention, endoscopic intervention, and or radiologic intervention

If yes, type of intervention or procedure: --

A7 Did the patient receive a blood transfusion associated with this complication?
-- / 1: Yes / 2: No

same as above

Annotated 26MAR2013

If yes, number of units of blood transfused:

Number of units should be in cc

A8 Was the patient admitted to the ICU as a result of this complication?

same as above

A9 Was the patient required to stay in the hospital for 14 days or more or 5 or more ICU days as a result of this complication?

same as above

A10 Did the complication cause the patient to experience residual disability or disease?

same as above

A11 Did the complication result in liver complications that caused the patient to be listed as a candidate for liver transplant?

same as above

If yes, date of listing:

Month Day Year

same as above

A12 Did the complication result in liver failure that led to transplantation?

same as above

A13 Did the patient die as a result of the complication?

same as above

Annotated 26MAR2013

Print

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Tasks

Hospitalization

Site ID:	902
Subject ID : Name	D4260 : M4vt0cuN, K2i/X0HK

Admissions less than 24 hours are not considered hospitalizations and should not be reported as such.

A1 Date of Admission:
Month Day Year

A2 Date of Discharge:
Month Day Year

A3 Was this admission associated with a study-tracked post-donation complication? (If yes, fill out Complication CRF.)
- --
- 1: Yes
- 2: No

Refer to the HRQOL Only Complication definition list for the complications being tracked in this study.

A4 Discharge Destination:
- --
- 1: Home
- 2: Hospital-affiliated transitional residence
- 3: Transfer to another hospital
- 4: Rehabilitation facility
- 5: Nursing home
- 6: Other
- 7: N/A (patient died)

A5 Number of days in ICU (enter "0" for none, leave blank if unknown):

If a subject spends overnight in the PACU this is considered 1day in the ICU. If a subject spends overnight in the PACU and one day in the ICU this is considered 2 days in the ICU

A6 Type of hospital:
- --
- 1: A2ALL hospital
- 2: Non-A2ALL hospital

A7 Type of hospital admission:
- --
- 1: Liver donation operation
- 2: Post-donation complication
- 3: Post-donation other

A8 (For post-donation complication or post-donation other) Primary discharge diagnosis (enter numeric ICD-9/10 diagnosis code):

Add the primary reason for this hospital admission. Use the discharge diagnosis ICD9 code, if more than one separate by a comma

Adult to Adult Living Donor Transplantation Study (A2ALL 2 Core)

HRQOL Only Donor Assessment training

Lahey, Pittsburgh, and Toronto
March 28, 2013

1

Roll Call / Introductions

- Lahey
- Pittsburgh
- Toronto
- DCC

A2ALL

2

A2ALL-2 Health-Related Quality of Life (HRQOL) Sub-Study Protocol

HRQOL Workgroup

Co-Chairs: ***Mary Amanda Dew, PhD, and*** **Zeeshan Butt, PhD**

Workgroup members: Daniela Ladner, MD, MPH, Andrea DiMartini, MD Susan Abbey, MD, April Ashworth, RN, David Axelrod, MD, James Burton MD, Brenda Gillespie, PhD, Susan Holtzman, PhD, Jan Jaeger, PhD, Anastasia Krajec, RN, Mary Ellen Olbrisch, PhD, Elizabeth Pomfret, MD, Mary Ann Simpson, PhD, Norah Terrault, MD, Robert M. Weinrieb, MD

Review of Completed Procedures

- Coordinators from each A2ALL-2 site have
  - Obtained consent from study participants. Maintained files with consent forms.
  - Sent contact info to their survey research site (PITT)
  - Worked with survey research team to troubleshoot problems with contact info or timing of surveys
  - Worked with survey team and site-specific clinical coordinators to arrange/facilitate care if study participant is deemed to be a danger to self or requests referral for care
- Coordinators from each A2ALL-2 site have not
  - Collected HRQOL survey data
  - Paid study participants for completing HRQOL surveys
  - Re-contacted study participants for any HRQOL follow up assessments

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Two HRQOL Cohorts of Subjects

- **Long term donors > 2 years post-donation followed in 3 successive waves of yearly surveys (HRQOL Only Subjects)**
- **Prospective donors surveyed prior to donation and then at 3, 6, 12 and 24 months following donation**

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Long Term Donors: Aim 1

Prevalence and trajectory of change in five HRQOL domains

- **Clinically significant psychiatric symptomatology**
- **Enduring fatigue, somatic symptoms, and lasting health concerns**
- **Negative changes in relationships**
- **Financial strains related to expenses, changes in employment, and insurance benefits.**
- **Reductions in global/overall HRQOL**

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Aim 2

To predict which donors are at risk for poor outcomes in the domains listed in Aim 1 examining

- Pre-donation characteristics (e.g. demographics, motivations for and ambivalence about donating)
- Medical factors (e.g. perioperative complications)

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Aim 3

To determine the prevalence rates and trajectory of change across time in

- Positive psychological outcomes of donation
- Satisfaction with donation
- Personal growth related to the experience

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Timeframe of Data Collection Impacting Analyses/Writing

- Last wave of long term donor follow-up concluding spring/summer 2014
  - First wave of surveys completed
  - 70% at second wave, none at third wave
- Data analyses have been partially completed for the first wave of surveys
- Medical record data collection from the 3 new sites

A2ALL

Complete Medical Record Review for Long Term HRQOL Donors

- Extraction of medical records on donors from the time of donation up to one year post donation, this includes :
- Collection of all HRQOL only study tracked complication and hospitalizations
- Examination of the medical records until 15 months post-donation to collect data on complications and hospitalizations within the first post-donation year
- This data will be collected in the A2ALL2 study data base A2ALLlink.

A2ALL

Review of Annotated HRQOL Only eCRFs and Data Elements

- HRQOL Only Donor Assessment eCRF
- HRQOL Only Donor Complication eCRF
  - Review HRQOL Only Complication list
- Donor Hospitalization eCRF

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11

HRQOL Only Donor Assessment eCRF

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12

HRQOL Only Donor Complication eCRF

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13

HRQOL Only- Study Tracked Complications

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14

Donor Hospitalization eCRF

A2ALL

15

HRQOL Only- Donor Study Tracked Complications

1: **Encephalopathy/hepatic coma** – Encephalopathy defined as liver-induced altered mental status or disturbed level of consciousness. This is based on diagnosis listed by examining physician; treatment is required in form of lactulose, neomycin, rifaximin or metronidazole therapy. This category includes hepatic coma.

2: **Ascites** - Defined as the presence of ascites by imaging or physical examination requiring the use of diuretics (typically furosemide, spironolactone, bumetanide or metalazone) or paracentesis. Physical examination or imaging study such as ultrasound/abdominal Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) should describe free intra-peritoneal fluid or presence of ascites.

3: **Liver cirrhosis** –Distortion of liver architecture with nodules surrounded by fibrous tissue. Requires documentation by histology. If no histology, then documentation of cirrhosis must be based on clinical criteria or labs.

4: **Liver Failure**- Defined as generalized deterioration of the hepatic function as manifested by the development of encephalopathy, renal insufficiency (serum creatinine >2, abnormal prothrombin time that is progressive and ultimately leads to listing for transplant.

5: **Liver Transplantation**-Defined as having received a liver graft for liver failure.

6: **Biliary stricture**: Presence of defined narrowing of the intrahepatic or extrahepatic bile ducts as radiologically identified by Endoscopic Retrograde Cholangiopancreaticgraphy **(**ERCP) or transhepatic cholangiography. A bile stricture may occur at any time after donation/txp surgery.

7: **Bile leak/biloma** - A bile leak is defined as a persistent bilious drainage beyond 7 days after surgery that may occur from the cut surface of the liver, from the donor's over sewn bile duct stump, or an unidentified accessory duct. The presence of bile leak is identified by the presence of bilious drainage beyond 7 days in the drain, outlined by a radiological study such as ERCP or transhepatic cholangiography, or identified during surgical exploration. Additionally a bile leak may manifest as a fluid collection of bile (biloma), which is identified on CT scan and may require either radiological or surgical intervention.

8: **Re-exploration during transplant/donation hospitalization** – An unplanned return to the operating room following the initial procedure. If an additional complication (such as a bile leak) was discovered, this should be recorded as an additional complication

9: **Dehiscence** - Wound dehiscence is a surgical complication in which a wound breaks open along the surgical suture.

10: **Neuropraxia** - Sensory or motor peripheral nerve dysfunction that results in altered sensations or loss of motor function in the absence of a central nervous system disorder. This mostly occurs in the upper extremity, but can also occur in the lower extremity.

11: **Intra-abdominal bleeding** - Any bleeding within the abdomen. If a patient experiences a series of bleeds over several days, but never fully recovers between them, this constitutes only "one" episode.

12: **Upper Gastro Intestinal (GI) bleed caused by ulcer** - This may be originating from the upper (esophagus, stomach, duodenum), diagnosed as caused by an ulcer.

13: **Upper GI bleed not caused by ulcer** - This may be originating from the upper (esophagus, stomach, duodenum), but is not diagnosed as caused by an ulcer.

14: **Lower GI bleed caused by ulcer** - Lower GI bleed (small intestine distal to the duodenum, colon or rectum) diagnosed as being caused by an ulcer.

15: **Lower GI bleed not caused by ulcer** - Lower GI bleed (small intestine distal to the duodenum, colon or rectum) not diagnosed as being caused by an ulcer.

16: **Deep vein thrombosis** - Presence of thrombosis of the lower extremities as verified by an imaging study such as ultrasound/Doppler with the requirement of post-operative anti-coagulation therapy.

17: **Portal vein thrombosis** - Portal vein thrombosis as proven by ultrasonography, angiography, CT angiography or Magnetic Resonance Angiogram (MRA) or detected during a surgical procedure.
18: **Inferior vena cava thrombosis -** as proven by ultrasonography, angiography, CT angiography or MRA or detected during a surgical procedure.
19: **Hepatic artery thrombosis -** Defined as loss of flow in the hepatic artery as determined by ultrasonography, angiography, CT angiography or MRA or intraoperative assessment of vessel.
20: **Prolonged ileus** - This is defined by delayed return of bowel function for > 7 days after surgery. This is manifested by the delay in oral intake, bowel movements, and/or prolonged nasogastric suctioning.
21: **Localized intra-abdominal abscess** - These may include collections that contain pus and are accompanied by peritonitis and or manifestations of infection such as fever or elevated white count. They are identified by CT scan, ultrasonography or during reoperation and require treatment such as antibiotic therapy, surgical or radiologic intervention. Clinically insignificant collections that are detected during routine radiologic studies, but do not require treatment, should not be documented as complications. If an intra-abdominal collection contains bile, it should be classified as a bile leak.
22: **Bowel obstruction** - This is manifested by the delay in oral intake, bowel movements, and/or prolonged nasogastric suctioning beyond 7 days after the initial operation in the presence of radiologic study documenting the absence of continuity of the GI tract. This may be treated by conservative measures (GI suctioning, Intravenous Fluids (IV fluids) or by surgical intervention.
23: **Hernia development - Diagnosis** of a new or worsening (from pre-transplant/donation) hernia.
24: **Peptic ulcer development –** The development of an ulcer in the lining of the stomach or the first part of the small intestine (duodenum) documented by endoscopy.
The diagnosis of C-difficile colitis, documented by a stool test and treatment is started.
25: **C-difficile colitis -**The diagnosis of C-difficile colitis, documented by a stool test and treatment is started.
26: **Myocardial infarction -** Interruption of the blood supply to an area of the myocardium causing necrosis. Diagnosis is made by new ST-segment elevation or Q waves on electrocardiogram (EKG) or with a ratio of CKMB: CK $\geq$ 2.5 or elevated troponin levels.
27: **Congestive heart failure -** The inability of the heart to maintain an adequate blood flow. This results in congestion of the blood in certain veins and organs with an inadequate blood supply to body tissues. Diagnosis is made by the presence of acute pulmonary edema or cardiomegaly on chest X-ray. If performed, an echocardiogram should demonstrate one or more of the following findings, depressed left or right ventricular systolic function on echocardiography, any regional wall motion abnormality, or left or right ventricular hypertrophy.
28: **Cardio-pulmonary arrest -** Defined as a sudden cessation of the heart with lack of respiration. Document only complete cardiopulmonary arrests that require cardio-pulmonary resuscitation (CPR). If the patient suffered from a respiratory arrest that was not accompanied by cardiac arrhythmias or cardiac standstill, do not record as a cardio-pulmonary arrest.
29: **Wound infection** - Defined in general as a body fluid or tissue sample with a positive laboratory culture result that is treated with an intervention. Surgical wound infection or deep intra-abdominal abscess which requires intervention. This may include hospitalization, antibiotics, bedside wound opening, or formal surgical intervention.
30: **Biliary tree infection** – Defined as a blood borne organism which is cultured in the setting of abnormal liver function tests or imaging study revealing biliary tract disease. Also included are fluid collections which contain bile and are believed to be in communication with the biliary tree. Defined in general as a body fluid or tissue sample with a positive laboratory culture result that is treated with an intervention.

31: **Blood infection** – Defined as a blood borne organism cultured with no other defined source. This would include bacteremia or fungemia presumed secondary to an indwelling line infection.
32: **Liver infection/abscess** - Intra-hepatic fluid collections which are determined to be an abscess as evidenced by positive culture of aspirated or drained fluid.
33: **Pulmonary infection** – Diagnosed by the presence of new or progressive focal pulmonary infiltrates on chest x-ray or CT scan, with some degree of pulmonary compromise (clinical symptoms of shortness of breath, signs of tachypnea, abnormal blood gas, ventilator requirement) and may be accompanied by purulent trachea-bronchial secretions, fever, leukocytosis, and/or a positive culture from sputum. A positive culture is not needed for this type of infection.
34: **Central nervous system infection** - Mental status changes or neurologic findings and an abnormal exam of cerebral spinal fluid. In the case of fungal infection, characteristic mass lesions on imaging are adequate.
35: **GI tract infection** – Defined as a positive stool culture for an organism located within the GI system. This also includes bacterial overgrowth in the small intestine, as documented by a breath test.
36: **Urinary tract infection -** Defined as a positive urine culture for an organism and treatment is started.
37: **Other infection location (specify)-**Defined as an infection in a location not noted in locations specified in complications #29-#36, above. Specify location in A2ALLlink.
38: **General psychological difficulties requiring treatment -** A new diagnosis for general psychological difficulties (excluding central nervous system (CNS)infection, depression or suicide attempt). This does not require an assessment by a mental health provider.
39: **Depression** - A new diagnosis or an increase in an existing history of depression, which requires treatment and/or hospitalization.
40: **Suicide attempt -** Defined as an attempt to intentionally cause one's own death.
41: **Pneumothorax -** Air or gas in the pleural space. Document only those resulting in chest tube placement.
42: **Pleural effusion -** Fluid in the pleural space. Pleural effusion is common in both living donors and recipients following donation or transplantation. Document only those resulting in chest tube placement or tapping of fluid.
43: **Pulmonary edema -** Accumulation of fluid in the interstitial lung tissues. Diagnosis is confirmed by a chest X-ray that is reported to show pulmonary edema, without other findings to suggest congestive heart failure.
44: **Respiratory arrest -** Respiratory arrest that required re-intubation and was not accompanied by cardiac arrhythmias or cardiac standstill. If CPR is not successful and the patient died, please document date and cause of death.
45: **Aspiration -** Aspiration of a sufficient volume of gastric acid produces a chemical pneumonitis with or without a secondary infection. Document the occurrence of sudden respiratory distress that may require intubation associated with the appearance of a new, focal infiltrate on a chest X-ray or suctioning of gastric contents from an endotracheal tube should intubation occur.
46: **Pulmonary embolus -** Patients should have sudden onset of dyspnea associated with tachypnea and tachycardia in the presence of a normal chest X-ray. Document those with a high probability for embolus V/Q scan or a spiral CT of the chest that demonstrates an embolus

Donor Study Tracked Complications – A2ALL-2 Core Protocol

1: **Encephalopathy/hepatic coma** – Encephalopathy defined as liver-induced altered mental status or disturbed level of consciousness. This is based on diagnosis listed by examining physician; treatment is required in form of lactulose, neomycin, rifaximin or metronidazole therapy. This category includes hepatic coma.

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28: **Cardio-pulmonary arrest -** Defined as a sudden cessation of the heart with lack of respiration. Document only complete cardiopulmonary arrests that require cardio-pulmonary resuscitation (CPR). If the patient suffered from a respiratory arrest that was not accompanied by cardiac arrhythmias or cardiac standstill, do not record as a cardio-pulmonary arrest.
29: **Stroke/CVA -** Defined as an interruption of the blood supply to any part of the brain. Documentation of Cerebrovascular disease; Cardiovascular Accident (CVA); Cerebral infarction; Cerebral hemorrhage; Ischemic stroke; Stroke - ischemic; Cerebrovascular Accident; Stroke – hemorrhagic, should be recorded as a stroke.
30: **Other Neurological Event** - Documentation of a neurological event, other than those listed.
31: **Wound infection** - Defined in general as a body fluid or tissue sample with a positive laboratory culture result that is treated with an intervention. Surgical wound infection or deep intra-abdominal abscess which requires intervention. This may include hospitalization, antibiotics, bedside wound opening, or formal surgical intervention.

32: **Biliary tree infection** – Defined as a blood borne organism which is cultured in the setting of abnormal liver function tests or imaging study revealing biliary tract disease. Also included are fluid collections which contain bile and are believed to be in communication with the biliary tree. Defined in general as a body fluid or tissue sample with a positive laboratory culture result that is treated with an intervention.
33: **Blood infection** – Defined as a blood borne organism cultured with no other defined source. This would include bacteremia or fungemia presumed secondary to an indwelling line infection.
34: **Liver infection/abscess -** Intra-hepatic fluid collections which are determined to be an abscess as evidenced by positive culture of aspirated or drained fluid.
35: **Pulmonary infection** – Diagnosed by the presence of new or progressive focal pulmonary infiltrates on chest x-ray or CT scan, with some degree of pulmonary compromise (clinical symptoms of shortness of breath, signs of tachypnea, abnormal blood gas, ventilator requirement) and may be accompanied by purulent trachea-bronchial secretions, fever, leukocytosis, and/or a positive culture from sputum. A positive culture is not needed for this type of infection.
36: **Central nervous system infection** - Mental status changes or neurologic findings and an abnormal exam of cerebral spinal fluid. In the case of fungal infection, characteristic mass lesions on imaging are adequate.
37: **GI tract infection** – Defined as a positive stool culture for an organism located within the GI system. This also includes bacterial overgrowth in the small intestine, as documented by a breath test.
38: **Urinary tract infection -** Defined as a positive urine culture for an organism and treatment is started.
39: **General psychological difficulties requiring treatment -** A new diagnosis for general psychological difficulties (excluding central nervous system (CNS)infection, depression or suicide attempt). This does not require an assessment by a mental health provider.
40: **Depression** - A new diagnosis or an increase in an existing history of depression, which requires treatment and/or hospitalization.
41: **Suicide attempt -** Defined as an attempt to intentionally cause one's own death.
42: **Pneumothorax -** Air or gas in the pleural space. Document only those resulting in chest tube placement.
43: **Pleural effusion -** Fluid in the pleural space. Pleural effusion is common in both living donors and recipients following donation or transplantation. Document only those resulting in chest tube placement or tapping of fluid.
44: **Pulmonary edema -** Accumulation of fluid in the interstitial lung tissues. Diagnosis is confirmed by a chest X-ray that is reported to show pulmonary edema, without other findings to suggest congestive heart failure.
45: **Respiratory arrest -** Respiratory arrest that required re-intubation and was not accompanied by cardiac arrhythmias or cardiac standstill. If CPR is not successful and the patient died, please document date and cause of death.
46: **Aspiration -** Aspiration of a sufficient volume of gastric acid produces a chemical pneumonitis with or without a secondary infection. Document the occurrence of sudden respiratory distress that may require intubation associated with the appearance of a new, focal infiltrate on a chest X-ray or suctioning of gastric contents from an endotracheal tube should intubation occur.
47: **Pulmonary embolus -** Patients should have sudden onset of dyspnea associated with tachypnea and tachycardia in the presence of a normal chest X-ray. Document those with a high probability for embolus V/Q scan or a spiral CT of the chest that demonstrates an embolus

Recipient Study Tracked Complications – A2ALL-2 Core Protocol

1: **Encephalopathy/hepatic coma** – Encephalopathy defined as liver-induced altered mental status or disturbed level of consciousness. This is based on diagnosis listed by examining physician; treatment is required in form of lactulose, neomycin, rifaximin or metronidazole therapy. This category includes hepatic coma.

2: **Ascites** - Defined as the presence of ascites by imaging or physical examination requiring the use of diuretics (typically furosemide, spironolactone, bumetanide or metalazone) or paracentesis. Physical examination or imaging study such as ultrasound/abdominal Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) should describe free intra-peritoneal fluid or presence of ascites.

3: **Liver cirrhosis** –Distortion of liver architecture with nodules surrounded by fibrous tissue. Requires documentation by histology. If no histology, then documentation of cirrhosis must be based on clinical criteria or labs.

4: **Biliary stricture**: Presence of defined narrowing of the intrahepatic or extrahepatic bile ducts as radiologically identified by Endoscopic Retrograde Cholangiopancreaticgraphy **(**ERCP) or transhepatic cholangiography. A bile stricture may occur at any time after donation/txp surgery.

5: **Bile leak/biloma** - A bile leak is defined as a persistent bilious drainage beyond 7 days after surgery that may occur from the cut surface of the liver, from the donor's over sewn bile duct stump, or an unidentified accessory duct. The presence of bile leak is identified by the presence of bilious drainage beyond 7 days in the drain, outlined by a radiological study such as ERCP or transhepatic cholangiography, or identified during surgical exploration. Additionally a bile leak may manifest as a fluid collection of bile (biloma), which is identified on CT scan and may require either radiological or surgical intervention.

6: **Re-exploration during transplant/donation hospitalization** – An unplanned return to the operating room following the initial procedure. If an additional complication (such as a bile leak) was discovered, this should be recorded as an additional complication

7: **Dehiscence** - Wound dehiscence is a surgical complication in which a wound breaks open along the surgical suture.

8: **Neuropraxia** - Sensory or motor peripheral nerve dysfunction that results in altered sensations or loss of motor function in the absence of a central nervous system disorder. This mostly occurs in the upper extremity, but can also occur in the lower extremity.

9: **Intra-abdominal bleeding** - Any bleeding within the abdomen. If a patient experiences a series of bleeds over several days, but never fully recovers between them, this constitutes only "one" episode.

10: **Upper Gastro Intestinal (GI) bleed caused by ulcer** - This may be originating from the upper (esophagus, stomach, duodenum), diagnosed as caused by an ulcer.

11: **Upper GI bleed not caused by ulcer** - This may be originating from the upper (esophagus, stomach, duodenum), but is not diagnosed as caused by an ulcer.

12: **Lower GI bleed caused by ulcer** - Lower GI bleed (small intestine distal to the duodenum, colon or rectum) diagnosed as being caused by an ulcer.

13: **Lower GI bleed not caused by ulcer** - Lower GI bleed (small intestine distal to the duodenum, colon or rectum) not diagnosed as being caused by an ulcer.

14: **Deep vein thrombosis** - Presence of thrombosis of the lower extremities as verified by an imaging study such as ultrasound/Doppler with the requirement of post-operative anti-coagulation therapy.

15: **Portal vein thrombosis** - Portal vein thrombosis as proven by ultrasonography, angiography, CT angiography or Magnetic Resonance Angiogram (MRA) or detected during a surgical procedure.

16: **Inferior vena cava thrombosis** - as proven by ultrasonography, angiography, CT angiography or MRA or detected during a surgical procedure.

17: **Hepatic artery thrombosis -** Defined as loss of flow in the hepatic artery as determined by ultrasonography, angiography, CT angiography or MRA or intraoperative assessment of vessel.
18: **Prolonged ileus** - This is defined by delayed return of bowel function for > 7 days after surgery. This is manifested by the delay in oral intake, bowel movements, and/or prolonged nasogastric suctioning.
19: **Localized intra-abdominal abscess** - These may include collections that contain pus and are accompanied by peritonitis and or manifestations of infection such as fever or elevated white count. They are identified by CT scan, ultrasonography or during reoperation and require treatment such as antibiotic therapy, surgical or radiologic intervention. Clinically insignificant collections that are detected during routine radiologic studies, but do not require treatment, should not be documented as complications. If an intra-abdominal collection contains bile, it should be classified as a bile leak.
20: **Bowel obstruction** - This is manifested by the delay in oral intake, bowel movements, and/or prolonged nasogastric suctioning beyond 7 days after the initial operation in the presence of radiologic study documenting the absence of continuity of the GI tract. This may be treated by conservative measures (GI suctioning, Intravenous Fluids (IV fluids) or by surgical intervention.
21: **Hernia development - Diagnosis** of a new or worsening (from pre-transplant/donation) hernia.
22: **Peptic ulcer development –** The development of an ulcer in the lining of the stomach or the first part of the small intestine (duodenum) documented by endoscopy.
The diagnosis of C-difficile colitis, documented by a stool test and treatment is started.
23: **C-difficile colitis -**The diagnosis of C-difficile colitis, documented by a stool test and treatment is started.
24: **Myocardial infarction -** Interruption of the blood supply to an area of the myocardium causing necrosis. Diagnosis is made by new ST-segment elevation or Q waves on electrocardiogram (EKG) or with a ratio of CKMB: CK $\geq$ 2.5 or elevated troponin levels.
25: **Congestive heart failure -** The inability of the heart to maintain an adequate blood flow. This results in congestion of the blood in certain veins and organs with an inadequate blood supply to body tissues. Diagnosis is made by the presence of acute pulmonary edema or cardiomegaly on chest X-ray. If performed, an echocardiogram should demonstrate one or more of the following findings, depressed left or right ventricular systolic function on echocardiography, any regional wall motion abnormality, or left or right ventricular hypertrophy.
26: **Cardio-pulmonary arrest -** Defined as a sudden cessation of the heart with lack of respiration. Document only complete cardiopulmonary arrests that require cardio-pulmonary resuscitation (CPR). If the patient suffered from a respiratory arrest that was not accompanied by cardiac arrhythmias or cardiac standstill, do not record as a cardio-pulmonary arrest.
27: **Stroke/CVA -** Defined as an interruption of the blood supply to any part of the brain. Documentation of Cerebrovascular disease; Cardiovascular Accident (CVA); Cerebral infarction; Cerebral hemorrhage; Ischemic stroke; Stroke - ischemic; Cerebrovascular Accident; Stroke – hemorrhagic, should be recorded as a stroke.
28: **Other Neurological Event** - Documentation of a neurological event, other than those listed.
29: **Wound infection** - Defined in general as a body fluid or tissue sample with a positive laboratory culture result that is treated with an intervention. Surgical wound infection or deep intra-abdominal abscess which requires intervention. This may include hospitalization, antibiotics, bedside wound opening, or formal surgical intervention.
30: **Biliary tree infection** – Defined as a blood borne organism which is cultured in the setting of abnormal liver function tests or imaging study revealing biliary tract disease. Also included are fluid collections which contain bile and are believed to be in communication with the biliary tree. Defined in general as a body fluid or tissue sample with a positive laboratory culture result that is treated with an intervention.

31: **Blood infection** – Defined as a blood borne organism cultured with no other defined source. This would include bacteremia or fungemia presumed secondary to an indwelling line infection.
32: **Liver infection/abscess** - Intra-hepatic fluid collections which are determined to be an abscess as evidenced by positive culture of aspirated or drained fluid.
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45: **Pulmonary embolus -** Patients should have sudden onset of dyspnea associated with tachypnea and tachycardia in the presence of a normal chest X-ray. Document those with a high probability for embolus V/Q scan or a spiral CT of the chest that demonstrates an embolus
46: **Primary graft non-function –** Progressive worsening of liver function as measured by elevated prothrombin time, with no explanation on a technical basis (no vascular thrombosis by Ultrasound), and need for re-transplant.
47: **Acute rejection -** Histological evidence of features of rejection that lead to adjustment of immunosuppressive therapy or treatment with pulse steroids or antibody agents. Resolution date for complication should be when bolus steroid/antibody are stopped or other immunosuppression is decreased.

48: **HCC recurrence -** Imaging of lesion either within the liver or other extrahepatic site that is suspicious for recurrent or metastatic disease. Tissue diagnosis is not necessary.

A2ALL-2 Core Protocol
(Amendment #3)

FREQUENTLY ASKED QUESTIONS (FAQ)

Hepatitis C Virus (HCV) Sub-study

1. **Question: How do we get the HCV eCRFs to populate in A2ALLlink?**
   Answer: Continuing Sites: HCV recipients from Cohort, who were not originally uploaded to A2ALL-*Link* for CORE (dead, re-transplanted, or lost to follow-up status in Cohort), were uploaded to A2ALL-*Link* with the subject type status of "HCV only". In order to get the HCV Flow eCRF to populate, you must enter a consent status of "Waiver of Consent". Other subjects that had been consented for Core with the diagnosis of HCV from Cohort who are greater than 3 years post-transplant, the HCV Flow eCRF, for screening of the HCV study will prepopulate in A2ALL-*Link*. Note: Coordinators will need to review the consent version that these subjects signed, to make sure that the HCV biopsy was included (Amendment 2.0)
   New Sites: Sites will need to review LDLT and DDLT transplanted subjects (Between January 1998 and August 31, 2010) who had at least one potential living donor evaluated (with PE at center) and had evidence of HCV at transplant. These subjects will be added to A2ALL-*Link* as new subjects with the subject status of "HCV Only". If the subject is either dead, re-transplanted, or lost to follow-up, the subject consent status will be entered as "waiver of consent". Living subjects will be approached for consent, and once the subject consent status is added, the HCV Flow eCRF will populate.
   Gap subjects enrolled into CORE, with HCV status at txp, will have the HCV Flow eCRF populate, once the subject reaches 3 years post-transplant. Sites will need to reconsent subjects with Amendment 3.0 version for inclusion of the HCV biopsy substudy. The subject's updated consent status should be entered into A2ALL-*Link*, under consent history.

2. **Question: Subjects are not eligible for the HCV study if they achieved SVR pre-transplant. What does this mean**?
   Answer: SVR stands for Sustained Viralogic Response. The definition for inclusion into the HCV sub study is non- detectable HCV RNA at least six months after end of treatment prior to transplant. Sites will need to review their subject's HCV treatment history and review HCV RNA lab values prior to transplant for completion of this question (A1 on Subject Flow eCRF).

3. **Question: On the "HCV Subject Flow" eCRF, question B2 asks if the subject has evidence of advanced cirrhosis. How do I answer this?**
   Answer: This is defined as an Ishak fibrosis stage ≥5 based on histology, or liver stiffness > 12.5 kPa by transient elastography, and/or advanced HCV disease based on clinical criteria (in patients who do not undergo liver biopsy or transient elastography). You may need to inquire with your PI or site Hepatologist if this is not clearly available by data review.

4. **Question: What date do I use for the "Date of Cirrhosis Assessment" on the HCV Study Info eCRF?**
   Answer: The instructions are included on the annotated eCRF and state:
   Date of cirrhosis assessment should be:
   1. Protocol Bx Date if applicable
   2. Date of Previous Biopsy, with diagnosis of cirrhosis
   3. If Alive w/o Re-txp, Date of completion of Advanced Disease eCRF
   4. If Alive w/Re-txp, Date of re-txp
   5. If Dead w/o Re-Txp, enter date of death
   6. If Dead w/ Re-Txp, enter date of Re-Txp.

5. **Question: Which patients in new and continuing sites need biopsy slides sent to Toronto for review (central read)?**
   Answer:
   - All Sites – biopsies done for this HCV >Year 3 study, includes those done prospectively, and those done within 12 months.
   - Continuing Sites – biopsies between shipment to UNC (month/year) and start of HCV >Year 3 study, only those with cirrhosis.
   - New Sites – biopsies of all patients included in chart review for HCV study showing cirrhosis, those done prospectively, and those done within 12 months of HCV study entry**.**

6. **Question: Which patients in new and continuing sites need blood samples, and what type of samples?**
   Answer: Consented subjects who are getting a > 3 year biopsy (Amendment 2 approved-and consent obtained), those who've had a biopsy within last 12 months, and those with a previous biopsy-with documented cirrhosis (with Amendment 3 approval-and consent). The types of samples to collect are those outlined in the protocol; serum and plasma, whole blood for DNA extraction is only collected if it wasn't collected previously.

7. **Question: If a subject dies greater than 90 days post-transplant but before year 1 how do we answer the questions pertaining to 1 year post-transplant (on "HCV Transplant Info" eCRF Question D1) ?**
   Answer: Enter information as if the subject was at year 1 post-transplant.

Donor Pain Sub-study

1. **Question: Should we list the names of the pain meds in the field by "other" for types of pain management?**
   Answer: No you do not list the names of the pain meds in any portion of the donor pain survey. Record all routes of pain management that have been in use for the subject since undergoing the donation surgery.

2. **Question: What do I do if I am unable to administer the donor pain survey within the window?**
   Answer: Document the attempts to administer the donor pain survey. Go to A2ALL-*Link* and complete Question C1 on the DNR on the Post-op Week 1" eCRF. Document the reason why the survey wasn't administered. Refer to the MOO on how to handle the paper form or electronic form, and transmission of the form to the DCC.

HRQOL-only Sub-study

1. **Question: We have a subject who has multiple complications during a hospitalization. Do I fill out a hospitalization eCRF for each complication?**
   Answer: If the complications were all during one continuous hospitalization, then you only complete one hospitalization eCRF for that hospital stay.

2. **Question: I notice in the subject's chart there are indications that the subject has a pleural effusion on x-ray. Do I count the x-ray findings as a "study tracked complication"?**
   Answer: If there is no evidence in the subject's medical record that the pleural effusion required a chest tube placement or tapping of fluid, then it does not meet the definition of a study tracked complication for a pleural effusion and you do not have to complete a "complication" eCRF.

General Questions

1. **Question: I have a recipient who had an LDLT in the GAP era (4/15/2010) and was re-transplant on 11/27/10, (The subject doesn't have HCV). Is this subject eligible for CORE**?
   Answer: Yes, with Amendment 2.0, this subject will have data collected under a waiver of consent, from the time of the first LDLT to the date of re-Txp. This subject may have been initially entered as "reached study end point", but with Amendment 2.0, this subject is eligible for chart review of data under the "waiver of consent". All complications and hospitalizations should be recorded accordingly, along with any study visits. Please update the subjects consent status in A2ALL-Link, leaving the previous consent history, as is.

2. **Question: If the same organism is found in both blood cultures and wound swabs on the same day, do we record both the blood infection and wound infection?**
   Answer: You would record the complications as 1) a blood infection, and 2) a wound infection. Two separate complications.

3. **Question: We recently had a donor return to the hospital for drainage of a collection. The D/C note gives "intra-abdominal abscess" as the diagnosis, but the cultures from the drain did not show pus or bacteria. So, this does not meet the definition of a "localized intra-abdominal abscess" for the study tracked complications, so does this mean I don't record anything as a complication?**
   Answer: You should speak with your PI on the issue and if he does not feel this was an abscess, but rather a collection of fluid, there will be no need for you to complete a complication eCRF as it does not meet the definition of a study tracked complication. However, since the subject was admitted to the hospital for the fluid collection, you will need to complete a hospitalization eCRF.

4. **Question: I have a patient who was hospitalized five times last year, each time with classic symptoms of cholangitis, treated with antibiotics, etc. but this lady has never had a positive culture. So, do I record these hospitalizations as being due to a ST complication? Can I record these episodes of cholangitis as complications or do I record any complications for these events.**
   Answer: If the subject was cultured each time and it was negative, you would not record as complications, and the hospitalizations would not be due to ST complications, but the ICD-9 Code to use would be 576.9 (unspecified disorder of biliary tract) for each of those hospitalizations.

5. **Question: We are a new site and with Amendment #3, can you tell me which subjects will need reconsenting?**
   Answer: Subjects will need reconsenting with the Amendment #3 consent if; 1) the HCV subject is eligible for the HCV study, and agrees to have biosample collection with or without a liver biopsy; 2) the eligible HCV subject agrees to have their previous liver biopsies that have not been sent for a central re-read by Dr. Adeyi.

6. **Question: Our last LDLT recipient was transplanted on June 19th and then underwent a re-exploration on June 25th. The subject was initially transplanted with no flow modulations, but modulations were performed during the re-exploration. We're hoping to capture the modulation information from the re-explorations as intra-op data. What do you think?**
   Answer: The modulation information from the re-exploration on June 25th can be captured on the "Post-Txp Week 1" eCRF, page 2 section B if it fits the question B1 regarding vein flow modulation.