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

Retrospective Study Protocol Number A2ALL-Retro-01

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1. Introduction

Adult to adult living donor liver transplantation (LDLT) is a relatively new procedure increasingly used at major transplantation centers. Too few cases are performed at any one center and approaches to the patient and donor are too diverse across centers to provide reliable and generalizable information on donor and recipient outcomes from individual centers. Therefore, the National Institutes of Health has 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 has established the Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL) that will conduct both retrospective and prospective studies of LDLT.

2. Background/Significance

Over the last 20 years liver transplantation has become the standard of care and the only cure for end stage liver disease. Its success has led to over 4,000 transplants performed yearly. But there are at least 17,000 patients on the transplantation list awaiting cadaveric liver donation. As the waiting list has expanded, waiting time has also grown. As a result, patient mortality has increased while awaiting transplantation, and patients are often critically ill by the time of transplantation. Among possible remedies, living donor transplantation has become widely accepted for pediatric transplantation. Adult-to-adult LDLT is a more challenging procedure and may be associated with greater risk to the donor because of the larger portion of liver that is required. Right lobe adult-to-adult LDLT is a recently developed procedure, but nearly a thousand have already been performed in the United States. Although still a small number relative to the several thousand adult cadaveric liver transplants performed annually, LDLT has the potential for changing the face of liver transplantation. Not only does LDLT avoid the lengthening waiting period for a cadaveric transplant, it greatly reduces the ischemic period of the transplanted organ, allows more time for evaluation of the donor, and changes the operation from an emergency into a scheduled procedure. The major disadvantage of LDLT is that it is a difficult and potentially fatal operation for the donor. It also provides the recipient with a smaller portion of liver than would have been received with cadaveric transplantation.

The research objectives of the A2ALL Study concern factors that influence the outcomes of adult-to-adult LDLT. Recruited into this longitudinal cohort study will be adult patients and potential donors being considered for LDLT. Recipients and their donors will be followed for sufficient time to determine outcomes related to LDLT. These outcomes will be compared with those of transplant candidates who are evaluated for but do not receive LDLT. The primary objective concerns comparison of morbidity and mortality of patients who receive LDLT with a group or groups of patients with similar illnesses and prognoses. It is also important to compare the outcomes after LDLT to those after cadaveric transplantation. Transplant physicians need this information on outcomes to advise patients and prospective donors. Therefore, sufficient patient and donor pairs will be recruited to determine whether recipients of LDLT have substantially different survival than non-LDLT recipients. A large number of donors and recipients

from several geographically distributed institutions will be necessary to reliably determine if outcomes are different with the two approaches.

These issues are best addressed through prospective data collection. But, the main outcomes of the A2ALL prospective data collection will not be available for at least 5 years. Therefore, to gain initial insights into outcomes associated with these procedures, a retrospective cohort or look back study has been designed to compare the outcomes of LDLT and cadaveric liver transplants and the outcomes for living liver donors beginning in 1998 at the nine participating transplant centers of the A2ALL study. In order to be conducted rapidly and efficiently, this study will rely exclusively on existing medical records and patient materials.

3. Study Objectives/Specific Aims

3.1. Overall Aim of the Retrospective Cohort Study

The primary study objective is to determine whether the *decision* to undergo LDLT is beneficial for the patients who choose LDLT. The principal hypothesis is that receipt of a living liver allograft leads to better long term outcomes for liver transplant candidates than *pursuit* of cadaveric transplant. This is a study of the decision to perform LDLT. Several different patient outcomes will be considered.

3.2. Comparison of mortality between LDLT and non-LDLT recipients

3.2.1. Primary Aim

To compare the survival distribution from time of identification of a potential living donor between those receiving an LDLT and those not receiving one.

3.2.2. Secondary Aims

To compare the survival of LDLT vs. cadaveric recipients from time of transplant.

To compare rejection episodes between LDLT and cadaveric transplant recipients.

1. To determine the incidence and severity of rejection episodes occurring within one year after transplantation in recipients undergoing LDLT.
2. To determine the incidence of steroid resistant rejection
3. To determine the incidence of recurrent rejection occurring within 1 year after transplantation

3.3. Retrospective Hepatitis C Virus (HCV) Study

3.3.1. Primary Aim

To determine if recurrent HCV disease at 1 yr (± 3 months), as observed histologically, is more severe in patients undergoing LDLT as compared to cadaveric transplant.

3.3.2. Secondary Aims

To compare the rate of fibrosis progression (comparison of 1 yr. and most recent biopsy) in LDLT and cadaveric transplant

To determine if cholestatic hepatitis in transplanted patients with HCV occurs at a higher rate following LDLT as compared to cadaveric transplant controls.

To determine if rejection requiring treatment occurs at a higher rate in HCV patients who undergo LDLT as compared to cadaveric transplant and to correlate this frequency of treatment of rejection to aggressive recurrence of HCV as defined histologically.

To compare rate of graft loss secondary to HCV between LDLT recipients and cadaveric recipients.

3.4. Retrospective Hepatocellular Carcinoma (HCC) Study

3.4.1. Primary Aim

To compare the outcomes for patients with HCC from the time of LDLT donor evaluation for those receiving LDLT versus those not receiving LDLT. Outcomes considered will include survival, hospitalizations, ablative treatments, and HCC status/recurrence.

3.4.2. Secondary Aim

To compare the demographic characteristics, HCC stage, and outcome (patient survival and cancer-free patient survival) in patients receiving LDLT or cadaveric transplant with HCC as either a primary or secondary pre-transplant diagnosis (excluding incidental tumors discovered at the time of transplant).

3.5. SRTR Data Validation Study

3.5.1. Primary Aim

To estimate the completeness and correctness of selected data elements submitted by the transplant centers to the Organ Procurement and Transplantation Network (OPTN) and subsequently transmitted to the Scientific Registry of Transplant Recipients (SRTR).

3.5.2. Secondary Aims

To ascertain which data elements collected via the OPTN data collection process can be reliably employed for use in the prospective A2ALL Cohort Study.

To provide feedback to the SRTR and OPTN on the accuracy and completeness of selected data elements.

3.6. Retrospective Post-surgical Complications Study

3.6.1. Primary Aim

To determine the rate of the major donor post-operative complications associated with planned right lobe liver donation

To compare the major recipient post-operative complications after LDLT versus cadaveric transplant.

3.7. Retrospective Resource Utilization Study

3.7.1. Primary Aim

To compare the resource utilization for patients who proceed to LDLT versus those for whom living donation does not occur and thus proceed toward cadaveric transplant.

4. Investigational Plan

4.1. Overall Study Design

Most of the specific aims require LDLT recipients and control patients who did not undergo LDLT. However, the identification of these controls and study start time (time 0) for following LDLT patients and controls will differ for the various objectives. All, or nearly all, of the LDLT recipients will be included in all analyses, which will simplify chart review. Many of the control patients will also be included in several analyses. LDLT donors will be evaluated for surgical complications.

For the primary survival and resource utilization objectives, the study entry point is at initial evaluation of a potential living donor that includes history and physical examination at the transplant center. The overall design of the retrospective cohort study is predicated on this definition as the starting point for inclusion in the cohort. In the primary analysis (see below), the mortality of LDLT patients will be compared to mortality of patients who have not yet had LDLT, regardless of subsequent events (cadaveric transplant, death, or removal from waitlist for any other reason). This cohort will include all those evaluated for LDLT transplants from 1/1/98 until 2/28/03. Among the 9 transplant centers in the A2ALL project, approximately 40% of individuals who had a potential living donor identified went on to undergo LDLT, leaving 60% as controls (see Feasibility Study report [Appendix A]). Based on this report, we estimate that approximately 800 patients were evaluated for LDLT at the 9 A2ALL transplant centers, of which approximately 300 subsequently received LDLT and 500 did not. A subset of this cohort with diagnoses of HCC at entry will also be used.

Other objectives regarding the post-transplant experience will compare LDLT to contemporaneous cadaveric transplants beginning at the time of transplantation. The analysis will control for center and date of transplantation as well as age, sex, disease (HCC, cholestatic, HCV/HBV, alcoholic, other), and severity of illness (MELD score, OPTN/UNOS status, CTP score). This comparison would involve approximately 300

LDLT recipients and approximately 250 cadaveric liver recipients. A subset of this cohort with diagnoses of HCV at entry will also be used.

Living donor liver transplantation presents unique immunological setting that is determined by three major variables that are different from the cadaveric setting, with the potential to impact on short and long term graft and patient survival. First, regeneration may be associated with different pattern of lymphocyte trafficking in and out the graft resulting in a differential repopulation of the liver with donor cells, and unknown effects on the extent of peripheral chimerism. Second, transplantation of a lobe from a living donor is done under conditions allowing extremely short cold ischemic time (60 vs. 500 minutes), a variable that may affect the severity of the inflammatory and immune response. Finally, it is estimated that 40% of LDLT are done in between genetically related individuals, resulting in a potentially more favorable HLA matching.

Previous single center studies have suggested a reduced rate of rejection after adult to adult LDLT. These observations should be validated by a carefully designed retrospective analysis of rejection rate and severity in AALDLT recipients. The clinical findings will determine the opportunities for appropriate clinical modifications in the immunosuppression protocol for the prospective study, aiming at better outcomes for graft rejection and recurrent disease. Moreover, they will set the stage for hypothesis-driven experimental studies, aiming to determine pattern of immune response and the potential development of favorable induction of tolerance.

For certain endpoints, supplementation of cadaveric controls above those identified in the retrospective cohort component of the study may be necessary. Augmentation with contemporaneous cadaveric controls would most likely occur for the first one to two years of a program's experience. If additional patients are required, they will be identified using SRTR data, frequency matching to the characteristics of recipients undergoing LDLT. Potentially, a few LDLT patients could be included in this group but excluded from the primary objective analysis. This situation would arise if a donor evaluation occurred in 1997, resulting in LDLT in early 1998, although this comprises a very small number of patients. We anticipate supplementation with no more than 100 to 200 transplant recipients.

The final cohort will include the LDLT donors (approximately 300).

4.2. Comparison of mortality between LDLT and non-LDLT recipients

4.2.1. Study Methods

The primary aim will use the cohort of subjects evaluated for LDLT. Survival from time of donor evaluation will be compared among those receiving and not receiving LDLT. In addition, we will compare both survival and rejection episodes for LDLT vs. cadaveric recipients from time of transplant.

Primary endpoint: Time of death or last known alive.

Secondary endpoint: Time from transplant to rejection episode, or last known time without rejection, incidence, number and severity of rejection and incidence of steroid-resistant rejection during the 1st post-transplant year.

4.2.2. Participant Selection

The cohort will include all of the following:
Potential recipient listed for liver transplantation

- age >= 18
- single organ

Potential donor evaluated with history and physical examination occurring between 1/1/1998 and the start date of the A2ALL-Cohort-01 Study enrollment. This date will be different for each clinical site and will be determined once site initiation is completed and the site is ready to begin enrollment of prospective subjects.

4.2.3. Data Elements

Two limitations of chart reviews must be kept in mind: Information may be missing, and information may be inaccurate. Because these problems can occur systematically, results can be biased. A2ALL will be circumspect about collecting information that is limited in either respect. Sample records will be examined for completeness and ease of obtaining information on all data elements before formal data collection begins.

a. At listing
Date of listing
DOB, sex, ethnicity (PHS categories)
Reasons for transplantation (list primary and secondary diseases)
MELD/UNOS status/CTP score at time of listing

b. Potential Donor
Date of each donor evaluation
Information on potential donor. Data collection on donors will largely be limited to clinically significant pre- and post-donation events and a small amount of operative information.
Donor outcome information
Reasons for not donating for those who do not donate

- Medical or psychological for donor
  - Medical condition (liver related vs. co-morbid medical conditions)
  - Anatomical
  - Size
  - Blood type
  - Psychological
- Donor declines/changes mind
- Recipient became too sick (or too well)
- Recipient received cadaveric transplant
- Other

Date of decision not to donate

c. Pre-transplant
Complications (treated ascites, treated SBP, variceal bleed, other GI bleeds requiring transfusion, hepatorenal, hepatopulmonary, treated encephalopathy, TIPS, portopulmonary hypertension, bony fracture [yes or no for each])
SBP Prophylaxis (yes/no)
Antiviral therapy (specific to HBV and HCV)
Changes in MELD, CTP, OPTN/UNOS status
Hospitalization admission and discharge date
Days in ICU
Death
Dates for each of these

d. Transplantation and beyond
Date of transplant
Selected intra-operative data
Hospitalization dates
Days in ICU
Retransplantation
Baseline immunosuppression regimen (tacrolimus, cyclosporine, or non-calcineurin antagonist based); antibody induction (yes/no)
Treated rejection episodes within one year of transplant:

1. Date of rejection (treated rejection episodes separated by less than 22 days will be considered the same event for analysis purposes).
2. Liver biopsy (when performed): Acute rejection severity as recorded in the original pathology reading (mild, moderate, severe or undetermined)
3. Immunosuppression at transplant and at the initiation of anti-rejection therapy
4. Drugs used to treat rejection

4.2.4. Sample Size and Power Calculations

We will compare the survival experience between those receiving a living donor liver transplant (LDLT) and those considered for an LDLT but not receiving one. Although the analysis will involve a fairly complex method of matching LDLT recipients with sets of non-recipients, for the purpose of power calculations, we will assume a much simpler 2-group design. We anticipate having at least 300 LDLT recipients and 500 non-recipients. Power calculations are based on the (two-sided) logrank test, an exponential survival distribution, and alpha=0.05. Assuming a one-year survival probability of 0.875 in the LDLT group, we have 82% power to detect as significant a survival probability among non-recipients as high as 0.83 or as low as 0.91, and 93% power to detect a survival probability among non-recipients as high as 0.82 or as low as 0.92.

For a comparison of rejection probabilities in the first year after transplant between LDLT (n=300) and cadaveric (n=250) transplants, we assume a two-sided test of binomial proportions with alpha=0.05. We also assume that approximately 32% of cadaveric transplants experienced a rejection episode. We will have 44% power to detect

a difference between LDLT and cadaveric transplants if the LDLT proportion is 25%, and 83% power if the LDLT proportion is only 21%.

4.2.5. Statistical Analysis

A comparison of survival between LDLT recipients and those evaluated for LDLT but not receiving a living donor organ will be made. An initial, approximate analysis comparing these groups will use Cox regression, with the time axis starting at time of donor evaluation, a time-dependent covariate for LDLT transplantation, and covariate adjustment for age, gender, race, calendar year of initial evaluation, liver disease etiology and severity, comorbidities and other variables. This analysis assumes that most candidates evaluated for LDLT either receive the transplant or do not receive it due to problems with the donor. In particular, it assumes that non-progression to LDLT due to cadaveric transplantation or because the recipient becomes too sick to transplant is rare. These assumptions can be evaluated when the data are available.

A second, more difficult but preferred analysis will be performed to compare survival from the time of LDLT surgery among LDLT recipients to a set of controls who were evaluated for LDLT, and were alive and eligible for transplant at the same time following donor evaluation as the LDLT patient was when they received their transplant. This analysis will involve a different set of controls for each patient, with many control patients re-used in several control sets. A modified Cox regression will be performed, with statistical adjustment for the re-use of controls. In both Cox analyses, variables will be checked to ensure that the proportional hazards assumption is met. If non-proportional hazards are detected, particularly for the LDLT effect, they will be modeled using time-dependent covariates. Interactions between covariates and the LDLT effect will be tested.

Survival from date of surgery for LDLT versus cadaveric transplant will also be compared using Cox regression, adjusted for prognostic variables. The distributions of time from transplant to rejection episode between LDLT and cadaveric transplant will be similarly compared.

We will also analyze the incidence, timing, and diagnosis (biopsy-proven or not) of clinically evident liver transplant rejection requiring treatment. Analyses of rejection will include subsets restricted to biopsy-proven and steroid-resistant rejection episodes.

4.3. Study of Hepatitis C Virus Infection

4.3.1. Study Methods

LDLT recipients transplanted for HCV will be compared to an approximately equal number of contemporaneous cadaveric controls selected from SRTR based on a diagnosis of HCV. If SRTR data are not complete for HCV identification, identification of HCV patients at the facility level may be required.

(Note: Post-transplant biopsies will be re-read by the local pathologist for grade, stage, and other characteristics of recurrent HCV. The biopsy performed closest to the one-year anniversary of transplant (+/- 3 months) will be employed for histologic scoring)

Primary end-point

a) Severity of disease based upon Knodell (necroinflammatory) and Ishak (fibrosis) scores on liver biopsy at 1 year (± 3 months) post-transplant in LDLT and cadaveric transplant.

Secondary end-points

a) Rate of fibrosis progression (comparison of 0, 1 year and most recent biopsy [the latter must be a minimum of 12 months after the 1-year biopsy] in LDLT and cadaveric transplants)
b) Proportion with cholestatic hepatitis
c) Proportion with treated acute rejection episodes
d) Graft loss due to recurrent hepatitis C

4.3.2. Participant Selection

All right lobe LDLT patients age >= 18 with documented positive HCV RNA prior to transplantation whose donors were evaluated between 1/1/1998 and the start date of enrollment into the A2ALL-Cohort-01 Study, and excluding those receiving anti-HCV positive or anti-HB_c positive organ. Cadaveric transplant controls transplanted for hepatitis C will be identified from cadaveric transplant controls in the retrospective study. Additional HCV-infected cadaveric transplant recipients will be identified by SRTR if there are insufficient matched controls in the retrospective study population. The analysis will adjust for center and time of transplant (both calendar time and time from donor identification).

Inclusion criteria

a) LDLT patients and cadaveric transplant patients with HCV
b) HCV RNA positive (within 12 months if no antiviral therapy or if HCV RNA positive post-transplant)

Exclusion criteria (cases and controls)

Anti-HCV positive controls who received anti-HBc positive or anti-HCV positive organs. Patients who are HCV RNA negative at last assessment prior to the time of transplant

Controls will be selected as above.

4.3.3. Data Elements

Verification of diagnosis with report of positive HCV RNA either pre- or post-transplant. Identification of anti-HB_c and anti-HCV status for both donor and recipient.

Histology 1 year post-transplant (± 3 mos), at start of antiviral therapy (if on treatment), and at last histological follow-up.

Data elements (donor and recipient) that will be collected for the retrospective study, plus the following:

Pre-transplant:

- HCV RNA level pre-transplant (within 12 months of transplant and in whatever units available – IU/mL preferred).
- HCV genotype
- History of antiviral therapy for hepatitis C prior to transplant (start and stop dates, specific therapy used, treatment response [ETR, SVR])
- HBV markers in recipient
- Graft size
- Donor age, BMI, steatosis, DM

Post-transplant (immunosuppressive therapy, treatment of rejection and other data collected as part of retrospective study)
HCV RNA levels at 1 year ± 3 months, at time of onset of cholestatic hepatitis, at time of re-transplant)

ALT levels (liver panel) within one month of transplant and at 1,3,6,9 and 12 months post transplant.
Antiviral treatment (start and stop dates, specific drugs and doses used and response [ETR, SVR])

Pre-transplant and post transplant treatment in both groups

HLA matching with donor

Pathology interpretation: Re-review by local pathologist and scoring using Knodell (necroinflammatory) and Ishak (fibrosis) scores.

Working definition of cholestatic hepatitis:

1. Bilirubin ≥4 mg/dl x 2 wks minimum, at least 8 weeks post-transplant, PLUS .
2. Pathology features of
   (i) cholestasis
   (ii) lobular or portal inflammation
   (iii) absence of features of acute rejection and chronic rejection. PLUS
3. Absence of the following:
   - hepatic artery thrombosis
   - biliary stricture
   - sepsis

4.3.4. Sample Size and Power Calculations

Primary endpoint: Comparison of Knodell (necroinflammatory) and Ishak (fibrosis) scores in LDLT or cadaveric transplant at 1 year post-transplant. Predictors of disease severity will be investigated using ordinal logistic regression analysis. We anticipate having at least 300 LDLT recipients and 250 cadaveric recipients, but only about 1/3 of these will have HCV prior to transplant. We assume sample sizes of 100 LDLT and 83 cadaveric recipients with prior HCV. Because sample size calculations for ordinal logistic regression are difficult, we base power calculations on a two-sample t-test (2-sided, alpha=0.05). For fibrosis score (0 to 6) as an outcome variable, we have 91% power to detect a difference of 0.5 in fibrosis score between LDLT and cadaveric recipients, assuming a standard deviation of 1.0.

Secondary endpoints: To compare rate of fibrosis in LDLT and cadaveric transplants (use last available biopsy). All biopsies scored for fibrosis using Ishak (0-6) and rate is based on time between transplant and last available biopsy. For the presence of severe histologic fibrosis at 1 year, we expect approximately 10% overall with bridging fibrosis (Ishak>=3). We will have 83% power to detect proportions as different as 0.05 for cadaveric transplant and 0.20 for LDLT, based on a chi-square test of equality of proportions with alpha=0.05.

We consider the power for comparing time to graft loss due to HCV based on a logrank test with alpha=0.05. We will have 84% power to detect a difference in the probability of graft loss at one year as large as 15% for LDLT versus 5% for cadaveric recipients.

4.3.5. Statistical Analysis

Fibrosis score will be analyzed using both ordinal and ordinary regression analyses, with the LDLT versus cadaveric recipients as the variable of primary interest. Ordinal logistic regression will be used to accommodate the ordinal nature of the fibrosis scale. Ordinary regression analysis will supplement the ordinal analysis and will facilitate interpretation, but does assume that the ordinal scale has roughly equal increments.

The proportions of patients with fibrosing cholestatic hepatitis and treated acute rejection episodes will be analyzed using chi-square tests of equality of proportions between LDLT and cadaveric groups. Logistic regression will be used to compare LDLT versus cadaveric transplants, adjusted for other covariates. Finally, time to graft loss will be analyzed using Cox regression, again comparing LDLT versus cadaveric recipients and adjusting for other prognostic factors. Graft loss or death due to causes other than HCV will be censored.

4.4. Study of Hepatocellular Carcinoma

4.4.1. Study Methods

LDLT recipients transplanted for HCC will be compared to HCC patients who had a donor evaluated for possible LDLT but who did not receive a LDLT. The analysis will adjust for cirrhosis etiology diagnosis, center, age, CTP/MELD score, use of ablation pretransplant, and pre transplant ablation method (i.e. chemoembolization, RFA, etc.). In

addition, a comparative analysis of LDLT and cadaveric transplant patients with HCC will be conducted.

4.4.2. Participant Selection

All right lobe LDLT patients age >= 18 whose donor was evaluated between January 1, 1998 and the start date of enrollment into the A2ALL-Cohort-01 Study at one of the A2ALL transplant centers, with patient diagnosis either primary or secondary of cirrhosis and HCC. Excluded subjects include any patient who was transplanted with a preoperative diagnosis of HCC and cirrhosis where no HCC was found at explant histology, and no prior ablation is recorded that may have caused complete necrosis of tumor leading to pathologic disappearance. For the comparative study of LDLT and cadaveric transplant recipients, no supplemental contemporaneous cadaveric controls will be used.

4.4.3. Data Elements

Maximum size and number by radiology pre-transplant and at transplant (explant)
Whether Milan criteria were met
Whether HCC was an incidental finding.
Date of diagnosis of disease recurrence post-transplant.
Number and type of HCC ablation procedures.

4.4.4. Sample Size and Power Calculations

We anticipate approximately 75 hepatocellular carcinomas among the ~300 LDLT cases, and approximately 125 among the ~500 non-LDLT cases who were also evaluated for LDLT. With 75 LDLT cases and 125 non-LDLT cases, we will have 90% power to detect a difference in recurrence (or presence) of HCC of 10% versus 30%. Since reduction of HCC in the non-LDLT group will be due to subsequent cadaveric transplantation, this statistical test will compare the strategy of LDLT versus waiting for a cadaveric transplant.

4.4.5. Statistical Analysis

Initial analysis of HCC will be primarily descriptive. The characteristics of HCC patients described will include TNM explant pathologic stage, use of ablation pretransplant, and pre transplant ablation method (i.e. chemoembolization, RFA, etc.). The proportion recurring within one year will be presented, with 95% CI. Predictors of one-year recurrence will be explored using logistic regression for patients with at least one year of follow-up. The difference between recurrence (or presence) proportions for LDLT versus non-LDLT patients will also be estimated using a 95% confidence interval. A comparison of survival between these two groups will be performed using Cox regression, adjusted for various prognostic covariates. A comparison of survival between LDLT and cadaveric transplant recipients will also be performed.

4.5. SRTR Data Validation Study

(This section does not apply to subjects who have the first living donor evaluated after 2/28/03)

4.5.1. Study Methods

We will investigate records for all patients with LDLT, and a subset of patients not receiving LDLT. These patients will be selected as needed to develop comparison cohorts for the other Retrospective research aims. All patients to be studied as part of any Retrospective cohort will be included in this validation study.

For each included patient, the A2ALL study coordinator will be asked to provide the data, based on chart review, for a selected subset of SRTR data items. The coordinator will be asked NOT to refer to copies of SRTR forms, but to provide the data based on chart review (or personal knowledge) alone. These data will be entered in a web-based data entry module. The module will have access to the original SRTR data, and will check the new data against the original SRTR data and provide immediate feedback if a discrepancy is found. The data coordinator will then resolve the difference, and either confirm the new value or enter a corrected value. The original SRTR record, as well as the final online entry, will be recorded in a special validation database.

The current SRTR data may be incomplete, and we have documented serious omissions in the reporting of HCC data. However, because the SRTR data were submitted closer to the time of listing and transplant, they may benefit from information available at those times that was not documented in the patient charts. Thus, if a discrepancy is found between the old SRTR data and the newly entered data, the coordinator will be given the opportunity to decide which is correct.

Potential for bias may arise if the A2ALL coordinator is the same person who enters the SRTR/OPTN data, or is a co-worker of that person. In that case, the A2ALL coordinator may be more likely to simply validate the SRTR data, rather than checking to make sure it is correct. We will attempt to minimize this bias by addressing the problem in the coordinator training session. Coordinators will be instructed in the importance of obtaining the data from chart review.

4.5.2. Participant Selection

All patients waitlisted for liver transplantation and considered for living donor transplantation between 1/1/1998 and 2/28/2003 at any of the nine A2ALL centers. If supplemental cadaveric transplant cases are used for any other specific aims, their data may also be included in the validation study.

4.5.3. Data Elements

Validation of SRTR data elements will incorporate information from patients included in all of the above studies.

4.5.4. Sample Size and Power Calculations

For an estimated proportion correct near 0.95 (95% correct), sample size of 300 will yield a 95% confidence interval (CI) for the true proportion will have a CI width of approximately +/- 0.025. For estimated proportions near 0.50 (50% correct), a 95% CI for the true proportion will have CI width of approximately +/- 0.057.

4.5.5. Statistical Analysis

The purpose of the data analysis is to document the correctness of the SRTR database. For each data element we will calculate: (1) the percent missing in the original SRTR data that were completed in the new data, (2) the percent of values that were not missing in the original data but were changed (corrected) in the new data, and (3) the percent of values that were correct in the original data. These percents should total 100%, unless an original SRTR data value was deemed to be incorrect and replaced with a missing value.

An additional analysis will investigate whether data quality changed after introduction of the electronic OPTN data submission system (UNet).

This validation study will tell us which of the SRTR data elements are reliable, and which are not. For each data element, we will assume that the A2ALL centers are representative of the other SRTR centers. Any data elements shown to be less than 95% correct in the A2ALL centers should be analyzed with caution in the full SRTR database.

We will also investigate center variability, to determine if error rates are center-specific or if they are similar across centers. This information will allow us to confidently use the full SRTR database for selected retrospective analyses.

4.6. Retrospective Post-surgical Complications Study

4.6.1. Study Methods

The major objective of this portion of the study is to define the incidence of donor morbidity in right lobe living donors in a retrospective cohort of patients and to compare recipient morbidity after LDLT or cadaveric transplant.

The charts of all right lobe donors will be retrospectively reviewed using a defined worksheet. The records of all patients who underwent a general anesthetic with the intent to proceed with living donation will be included. This will allow us to capture patients whose donation was aborted for various reasons. The hospital records, as well as any outpatient ambulatory medical records, will be included in the review. Visits to outside medical groups including visits to the emergency room department at other hospitals will be documented. Also, any subsequent medical care, such as physical therapy, will also be noted. It is the intent of this process to be inclusive of all potential complications that either required intervention or continuous monitoring. No control group will be used.

For the study of recipient complications, treated post-transplant complications (bile leaks, re-operation, treated rejection, and treated CMV infection) will be examined. The recipient complications study will focus on post-operative complications requiring intervention.

4.6.2. Participant Selection

All donors who were evaluated for right hepatic lobectomy between 1/1/1998 and the start date of enrollment into the A2ALL-Cohort-01 Study at any of the nine A2ALL centers and subsequently underwent the procedure will be included. All waitlisted

candidates for liver transplantation who had a potential donor considered for living donor transplantation and subsequently underwent either an LDLT or cadaveric transplant will be included. Supplementation of contemporaneous controls above those identified in the cohort component of the study may be necessary. If additional patients are needed, they will be selected using SRTR data. Controls will be frequency matched on center and date of transplantation (6 month window). In analysis, we will control for these variables as well as age, sex, disease (HCC, cholestatic, HCV/HBV, alcoholic, other), and severity of illness (MELD score, OPTN/UNOS status).

4.6.3. Data Elements

Data elements for the donor morbidity study will be taken from a donor morbidity/outcomes worksheet. Data elements for the comparative study of recipient morbidity will be taken from a recipient morbidity data collection form.

4.6.4. Sample Size and Power Calculations

Estimation of proportions of donor complications will be made using 95% confidence intervals (CI) based on the binomial distribution. Assuming 300 donors, 95% CI widths will be no larger than +/- 0.057.

Comparisons of recipient complications after LDLT and cadaveric transplants will be based on chi-square tests of equality of proportions. Assuming n=300 LDLT, n=250 cadaveric, and alpha=0.05, we will have 89% power to detect a difference in the proportion of bile leaks, for example, of 0.18 in the cadaveric group versus 0.30 in the LDLT group (a difference of 0.12). Physician estimates of this difference are closer to 0.20, so power is more than sufficient for this endpoint. If we more conservatively assume complication proportions near 0.5, we will have 89% power to detect a difference of 0.14 (such as 0.43 versus 0.57).

4.6.5. Statistical Analysis

Analysis of LDLT donor post-operative complications will be descriptive. We will report the proportions of donors with complications such as bile leak, primary non-function, graft failure, pneumonia, and urinary tract infection, as well as any complication requiring hospital admission, re-operation, or other intervention. Confidence intervals will be included with all estimates. We will also report follow-up outcomes including wound healing, pain medications, blood laboratory values, and the proportion of patients who returned to work/school. Some attempt will be made to correlate complications with patient characteristics and operative procedures, but any such analyses will be limited by the quality of available data.

LDLT recipient post-operative complications will be reported in the same way as the donor complications described above. In addition, a comparison of LDLT complications with complications following cadaveric transplant will be made. Depending on the type of complication (event occurrence, time to event, or continuous outcome), a comparison of the events between LDLT and cadaveric transplants will be made using logistic regression, Cox regression, or ordinary regression, respectively, each adjusted for other predictive variables as needed.

4.7. Retrospective Resource Utilization Study

4.7.1. Study Methods

Length of hospitalization, days in ICU, and major interventions will be used as measures of resource utilization. Note: Incorporation of cost and charge data is not planned. Such information is both difficult to obtain and to interpret.

4.7.2. Participant Selection

The cohort will include all of the following:
Potential recipient listed for transplantation

- age >= 18
- single organ

Potential donor evaluated between 1/1/1998 and the start date of enrollment into the A2ALL-Cohort-01 Study.

4.7.3. Data Elements

Hospitalization admission and discharge dates (pre-transplant and post-transplant). Number of ICU days. Major interventions performed during inpatient hospitalizations

4.7.4. Sample Size and Power Calculations

For comparing hospitalization between LDLT recipients and non-recipients we consider the number of hospital days in one year. Although the analysis will take into account the possibility that some patients may be included in both groups, both pre- and post-LDLT, the power calculations consider a similar but simplified design based on a two-sample t-test (2-sided, alpha=0.05), assuming 300 LDLT recipients and 500 non-recipients. We have no preliminary data on means or standard deviations (s.d.s) for number of hospital days in a year, but assuming a fairly large s.d. of 25 days, we will have 93% power to detect a difference of 5 days (effect size = 0.20 s.d.) between LDLT and non-LDLT groups.

4.7.5. Statistical Analysis

Resource utilization, particularly hospitalization (number of hospitalizations and number of hospital days) will be compared for those with and without LDLT using a repeated measures logistic regression analysis. In addition, a comparison of hospitalization after LDLT versus cadaveric transplant will be made.

5. Human Subjects

5.1. Protection of Human Subjects

5.1.1. Institutional Review Board

This data collection 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 IRBs for approval prior to implementation.

Each center will complete an application to their own IRB to allow receipt of the center-specific SRTR-identified data set and the abstraction of additional information from the medical record and release of this identified information to the DCC for analysis. The application will request a waiver of written informed consent for this retrospective project. The DCC will also have in place an IRB approved protocol to complete its responsibilities for the study. The DCC will, in turn, receive identifiable data from the centers to allow for linking to the prospective study in the future to avoid the need for duplicative data collections.

In order to plan a successful prospective study it is important to include all adult-to-adult donors and recipients of living donor liver transplants. Because the numbers are large and span a five-year period it would be extremely difficult to obtain written informed consent for all subjects in the data set. Therefore, each transplant center will request a waiver of informed consent for this data collection and release of patient identified information. The following paragraphs delineate the rationale for requesting a waiver of informed consent for the retrospective study.

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 be 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 retrospective study meets the above four criteria necessary for consideration of a waiver of consent.

1. The research will abstract information that was collected in standard medical records during routine medical evaluation and follow-up. The risk to the subject 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 University of Michigan computer system.

2. A waiver of written informed consent will not adversely affect the rights or welfare of the research subjects. These data will consist of routine laboratory and procedure results, complications and outcomes of surgery and overall level of health that have been recorded in the subject's medical record. It is important to keep this data linked to the subject to avoid the need to "recollect" the data for use in the planned prospective clinical trial.

3. The inclusion of every living donor liver recipient and donor from each of the A2ALL transplant centers is necessary for the planning the prospective study. There are well-documented investigations of the bias introduced by the informed consent process. In order to avoid this bias and examine the overall effect of this procedure, every patient that has participated in this procedure must be examined. Successfully locating, contacting and securing informed consent from each subject is "impracticable". The results of this retrospective analysis will guide the development of a 5-year prospective longitudinal investigation of this study population. All eligible retrospective study subjects will be approached and informed consent will be documented for the prospective study. Only the retrospective study subjects that are able to be contacted and provide written informed consent will be enrolled into the prospective study.

4. Information that is revealed from this study will be presented at transplant meetings and published in scientific periodicals. The NIH will also utilize press releases to communicate the study findings. In this manner, information that may affect the previous subjects will be communicated.

Additionally, this study meets the requirements for a waiver of consent under the new HIPAA guidelines.

The HIPAA requirements for a waiver of consent (164.512(i)(2)(ii)) are:

1. No more than minimal risk to subject *(addressed above)*

2. Plan to protect identifiers from improper use/disclosure

   Secure web servers and limited access to the data will protect the data from improper use/disclosure

3. Plan to destroy identifiers at earliest opportunity consistent with conduct of research unless retention required by law or research design

   The links will be removed as soon as determination of ability to contact subject for prospective study has been made. Any subject contacted and not interested in participating, any subject that is deceased and any subject that can not be located

will have identifiers destroyed. The remainder will have the links maintained after consent is obtained and they will be enrolled into the prospective study. Data sets for this retrospective study will be coded and have identifiable information removed prior to analysis by the DCC.

4. Written assurances that Private Health Information (PHI) will not be reused or disclosed except as required by law or oversight

   The DCC will provide a written assurance that the information will be not reused or disclosed.

5. Can't do research without waiver

   Significant bias introduced without waiver is addressed above.

6. Can't do research without access to and use of PHI.

   The need to link to potential prospective data in the next study is discussed above. The DCC will be requesting data sets from the SRTR that contain identifiable information and will distribute these to the individual transplant centers that originally submitted the data. The DCC will receive the data set back from the transplant centers with corrections and additions of the original data as well as additional data elements obtained from medical record review. The DCC will maintain these links until the prospective study begins and will destroy the links for non-participators in the prospective study. At all times the data will be stored and transferred via secure data servers that require username and password access.

5.1.2. Patient confidentiality

Special procedures for ensuring patient confidentiality will be implemented. Data transmission and the distributed data systems have multiple layers of security as discussed in the study management section. Each study subject will be assigned an identification number. Only this number will be used to identify subjects in any individual tabulation. 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. These passwords will be changed on a quarterly basis and whenever the Database Administrator makes a determination for a security change. 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 Institute 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.

5.1.3. Risks to the patient

This data collection represents no more than minimal risk to the subjects and does not contain sensitive information. All data scheduled for collection and analysis have already been collected and documented as a part of standard clinical care. It would be impracticable to find, contact and obtain informed consent from each subject in the study group. This study meets the federal guidelines for a waiver of informed consent.

5.1.4. Unauthorized data release

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 but would be a serious invasion of the subject's privacy. 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. It is envisaged that the DCC will provide a second level of security checks. Data to be used for analysis will contain only the assigned identification numbers. All patient identifiers such as name, address and hospital record identification number will not be accessible to the staff involved in carrying out data analysis.

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. The demographics of the study population are pre-determined due to the retrospective all-inclusive nature of the study. Women will be included in the retrospective study as living liver donors and 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. The demographics of the study population are pre-determined due to the retrospective all-inclusive nature of the study. Racial and ethnic minority groups will be included in the donor and recipient components of the retrospective study and will be proportional to their representation in the donor and recipient population.

5.5. Inclusion of Children

The Adult-to-adult living donor liver transplantation cohort study specifically excludes children.

5.6. Data and Safety Monitoring Plan

Accepted principles of data and safety monitoring will be observed throughout the conduct of the A2ALL retrospective study. Since the retrospective study is restricted to review of information in the medical record, no adverse events will occur or be reported.

Each transplant center principal investigator will be responsible for monitoring the A2ALL retrospective study, as will the DCC. Monitoring responsibility will extend to determination of accurate and effective conduct of the protocol and to recommendations regarding closure of the study.

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 way and 3) recommendations that result from study monitoring are completed.

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.

6. Study Organization

6.1. 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.

1. Columbia University Health Sciences
   New York, NY
   Principal Investigator: Jean Emond, MD
2. Northwestern University
   Chicago, IL
   Principal Investigator: Michael Abecassis, MD
3. University of Pennsylvania
   Philadelphia, PA
   Principal Investigator: Abraham Shaked, MD
4. University of Colorado Health Sciences
   Denver, CO
   Principal Investigator: James Trotter, MD
5. University of California, Los Angeles
   Los Angeles, CA
   Principal Investigator: Mark Ghobrial, MD

6. University of California, San Francisco
   San Francisco, CA
   Principal Investigator: Christopher Freise, MD
7. University of North Carolina
   Chapel Hill, NC
   Principal Investigator: Roshan Shrestha, MD
8. University of Virginia
   Charlottesville, VA
   Principal Investigator: Carl Berg, MD
9. Virginia Commonwealth University
   Richmond, VA
   Principal Investigator: Robert Fisher, MD

6.2. 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.

University of Michigan
Ann Arbor, MI
Principal Investigator: Robert M. Merion, MD

6.3. 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 Scientist. 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.

6.4. Retrospective Study Subcommittees

The following subcommittees have been established to address specific issues in the Retrospective study.

- Retrospective Protocol Design

- Hepatitis C Virus (HCV) Workgroup
- Hepatocellular Carcinoma (HCC) Workgroup
- Outcomes/Endpoints/Definitions Workgroup

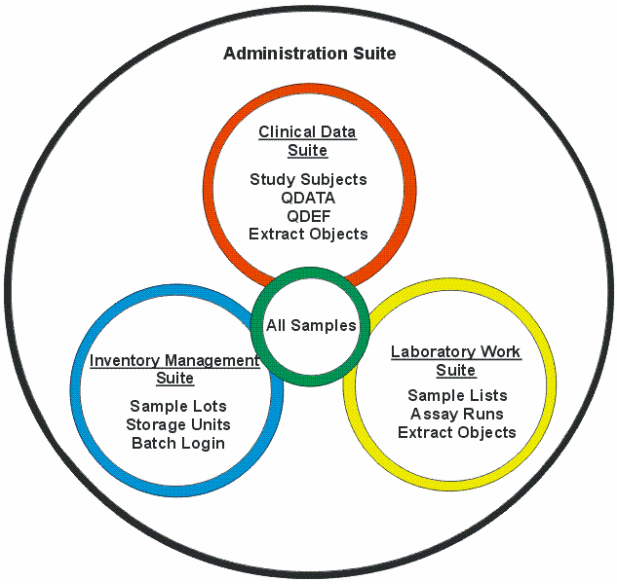
Other possible subcommittees include:

- A2ALL Study Policies
- Ancillary Study Policy
- Publication and Presentations
- Access to Study Data
- Others as required

7. Study Management

7.1. Data collection, Data Collection Forms, and Data Entry – BioDBx

The DCC will utilize the web-based BioDBx program as the data management nucleus for the A2ALL studies. This system, developed specifically for multicenter clinical trials management, was created by Dr. Stephen Gruber and Mr. Joseph Bonner at the University of Michigan, both of whom will be participating as consultants to the DCC. Briefly, BioDBx 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. There are three main suites: the Clinical Data Suite, which manages clinical data, the Inventory Management Suite, which manages inventory such as acquired specimens, and the Laboratory Workspace, which manages laboratory operations. An Administrative Suite is the overall manager for the foregoing three suites.



The Clinical Data Suite manages clinical data within a defined hierarchy, the highest level of which is termed Active Studies. From Active Studies, study subjects and study data are managed and clinical data can be viewed. There is a QDef module where study set-up occurs and a QData module where clinical data are entered after being defined by QDef. The Study Subjects module is used to enter and manage demographic data for study participants and the Study Samples module allows entry and edit of data for samples obtained from the subjects in the study.

The primary mechanism by which a study is set up in BioDBx is through a four-component QDef (Question Definition) module. The four components are: 1) definition,

2) validation, 3) extraction, and 4) navigation. Definition functions to determine where and why a variable or question appears. Validation determines acceptable values for a variable or acceptable answers to a question. Extraction defines where the data from a particular element will go for statistical analysis. Navigation is a characteristic that determines what data element is requested next.

QData is the module within the Clinical Data Suite used to enter and edit data from Case Report Forms or study questionnaires. QData can only be utilized for a given study when the entire battery of questions for a study have been defined (in QDef) and tested. For the complement of data defined, QData prepares individual data entry screens for users to key responses for specific study subjects. After responses have been entered, they can be printed and reviewed or extracted into extract objects for statistical analysis.

The DCC will utilize the BioDBx QDef module to create electronic case report forms to capture all relevant study data for the main A2ALL cohort study, the study of previously transplanted A2ALL recipients, the A2ALL donor study, and all investigational/research protocols that are developed and implemented during the course of the study. The BioDBx system allows real-time monitoring of study data for protocol adherence, quality assurance, adverse event reporting, discrepancy reporting, and other trends.

7.2. Data Management

All study data will be entered into the BioDBx electronic data entry system by study coordinators at each study site. This data will be encrypted and transferred to the DCC and stored on a secure server at the University of Michigan. Access to the server and BioDBx system is 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 the data sets will utilize de-identified (coded) data sets.

7.3. 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 BioDBx 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 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, the Clinical Monitor or Project Manager 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 Monitor and Project Manager will produce reports from the BioDBx system 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.

7.4. Data Security/Data Transfer

Personnel at each study center will collect and enter data into BioDBx, a web-based data entry system. Authentication is currently enabled from Oracle Developer Form Server to the Oracle database. Between the web server and client browser, secure socket layer technology is in place. This will ensure safety and confidentiality of data by using secure encrypted data transmission from the transplant centers to the BioDBx database server.

The database logs every modification of every cell in the database to ensure the ability to monitor access to the data and audit transactions. The system is accessible only via an established account with a logon and password for security and confidentiality. Authorized study personnel will be assigned an account on the system. Passwords will have defined expiration dates and must be changed regularly to permit continuing access.

The BioDBx database server is located in a locked cabinet in a locked room at the University of Michigan Medical Center. The hardware administrator and his designated backup are the only individuals who have keys. The data will be transferred via the secure network to the Kidney Epidemiology Cost Center (KECC) at the University of Michigan. The A2ALL project staff is physically located in the KECC office suite. The office suite is kept locked with entry control 24 hours a day to prohibit unauthorized entry.

The computer system at KECC currently is used for research projects that involve processing large volumes of identified and re-identifiable patient-specific data. The KECC system has a comprehensive security plan based on the guidelines in OMB Circular A-130, "Security of Federal Automated Information Resources" and NIST Publication 800-18 "Guide for Developing Security Plans for Information Technology Systems." This plan has undergone extensive review by HRSA for security certification for maintaining patient-identified data. The A2ALL project will be covered by this security plan and will be required to comply.

8. Procedures and Instructions

BioDBx will be utilized for electronic submission of data for this study. Detailed instructions on the use of BioDBx, 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.

9. Expected Publications

A. Mortality and major morbidity consequent to choosing LDLT (primary objective)
B. Recurrence of and other outcomes of hepatitis C post-LDLT
C. Descriptive experience of post-LT HCC outcomes according to pre-LDLT variables.
D. Donor complications
E. Post-LDLT recipient outcomes (requires prospective identification of the outcomes that would be reported).
F. Validation of SRTR (a longer report could be provided to HRSA, OPTN)

APPENDICES

Appendix A. Feasibility Study

Summary	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	35	27	77%	4	11%	4	11%	0	0%
1999	99	54	55%	26	26%	16	16%	3	3%
2000	155	61	39%	37	24%	28	18%	29	19%
2001	275	99	36%	53	19%	40	15%	83	30%
2002	298	94	32%	61	20%	19	6%	124	42%
Total	862	335	39%	181	21%	107	12%	239	28%

Northwestern	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	0	0		0		0		0	
1999	5	2	40%	2	40%	1	20%	0	0%
2000	17	7	41%	4	24%	2	12%	4	24%
2001	13	9	69%	1	8%	2	15%	1	8%
2002	23	10	44%	6	26%	3	13%	4	17%
Total	58	28	48%	13	23%	8	14%	9	16%

VCU	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	17	12	71%	1	6%	4	24%	0	0%
1999	36	25	69%	5	14%	4	11%	2	6%
2000	16	11	69%	3	19%	1	6%	1	6%
2001	21	7	33%	3	14%	7	33%	4	19%
2002	29	9	31%	4	14%	1	3%	15	52%
Total	119	64	54%	16	13%	17	14%	22	18%

1071

UVA	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	0	0	0%	0	0%	0	0%	0	0%
1999	6	3	50%	3	50%	0	0%	0	0%
2000	10	6	60%	3	30%	1	10%	0	0%
2001	16	9	56%	3	19%	3	19%	1	6%
2002	7	3	43%	2	29%	1	14%	1	14%
Total	39	21	54%	11	28%	5	13%	2	5%

UNC	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	4	2	50%	2	50%	0	0%	0	0%
1999	17	9	53%	7	41%	1	6%	0	0%
2000	25	6	24%	4	16%	7	28%	8	32%
2001	31	5	16%	8	26%	4	13%	14	45%
2002	12	1	8%	5	42%	0	0%	6	50%
Total	89	23	26%	26	29%	12	14%	28	31%

Penn	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	0	0		0		0		0	
1999	3	2	66%	1	33%	0	0%	0	0%
2000	17	5	29%	2	12%	8	47%	2	12%
2001	15	5	33%	5	33%	4	27%	1	6%
2002	12	7	58%	2	16%	0	0%	3	25%
Total	47	19	40%	10	21%	12	26%	6	13%

1072

Colorado	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	0	0		0		0		0	
1999	0	0		0		0		0	
2000	0	0		0		0		0	
2001	35	19	54%	7	20%	4	11%	5	14%
2002	24	9	38%	6	25%	0	0%	9	38%
Total	59	28	47%	13	22%	4	7%	14	24%

UCLA	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	0	0		0		0		0	
1999	18	2	11%	6	33%	9	50%	1	6%
2000	28	6	21%	8	29%	6	21%	8	29%
2001	32	12	38%	5	16%	8	25%	7	22%
2002	41	7	17%	9	22%	6	15%	19	46%
Total	119	27	23%	28	24%	29	24%	35	29%

UCSF	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	0	0	0%	0	0%	0	0%	0	0%
1999	1	0	0%	1	100%	0	0%	0	0%
2000	17	6	35%	7	41%	3	18%	1	6%
2001	66	21	32%	15	23%	5	8%	25	38%
2002	103	23	22%	18	18%	6	6%	56	54%
Total	187	50	27%	41	22%	14	7%	82	44%

1073

Columbia	Total	Received LDLT		Received CAD		Died/Removed from List		Still Waiting	
Year	LDLT Candidates	Number	%	Number	%	Number	%	Number	%
1998	14	13	93%	1	7%	0	0%	0	0%
1999	13	11	85%	1	8%	1	8%	0	0%
2000	25	14	56%	6	24%	0	0%	5	20%
2001	46	12	26%	6	13%	3	7%	25	54%
2002	47	25	53%	9	19%	2	4%	11	23%
Total	145	75	52%	23	16%	6	4%	41	28%

1074