ACUTE LIVER FAILURE STUDY GROUP
MANUAL OF OPERATIONS

A Multi-Center Group to Study Acute Liver Failure: Including Acute Liver Injury

14th Edition

Protocol v6
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The Manual of Operations and Procedures (MOP) has been written to provide physicians, nurses, coordinators and others involved in the Acute Liver Failure Study Group (ALFSG) with a detailed step-by-step description of the entire study. It is important that Study Coordinators and Principal Investigators (PI) at each of the participating sites become familiar with the entire contents of the MOP. Should you have further questions or need clarification, please do not hesitate to contact someone from the Core Administrative center.

ALF Registry
Contact Information

Topic	Contact Person
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INTRODUCTION

Purpose

Acute liver failure (ALF) is a unique illness of multiple etiologies, unusual severity and a rapid clinical course. Even when the etiology is known, the reasons for the fulminant nature of the disease in a given individual (hepatitis B, for example) remain unknown. The Acute Liver Failure Study Group (ALFSG) was organized in 1997 around the idea that a disease this devastating and this infrequent (estimated 2,000 cases per year in the U.S.) can only be studied effectively by gathering data and evaluating treatments using multiple centers around the United States.

ALF Study Group Infrastructure and Study Design

The initial grant application was submitted in October 1, 1996, and funded on September 1, 1997 for a two-year period. The award stipend was $50,000, plus indirect costs for each of the two years. This stipend was divided into salary for the PI, the administrative assistant, office of biostatistics (form design, data management), and limited support of meetings and travel. Unfortunately, no money was available to individual sites during the planning grant period. Funding from the FDA has provided a small amount per patient enrolled in the N-Acetyl Cysteine (NAC) pilot study (for up to 50 patients) and additional funding for data entry and analysis. The RO1 grant, funded September 1, 2000 adequately supported all the study sites per patient enrolled in the data and serum collection study and an additional amount per NAC patient. At the end of the first phase of the study (2 years of data and serum collection), a number of other satellite and collaborative projects are under way including the development and testing of new prognostic models, and provision of serum samples to investigators searching for new viruses. To date tests run have included SEN V virus, hepatitis B, alpha-fetoprotein, S100ß and Gc protein. Later studies might be directed toward the testing of new liver assist devices. The future is limitless in terms of the variety of studies in which the group may participate, and it is ultimately up to the group to decide its direction and project choices.

William M. Lee, MD is the principal investigator. The initial grant was written by Dr. Lee with help from Frank Schiødt, MD, a Danish visiting fellow. George Ostapowicz, MD served as the “chief operating officer” of the study for more than 2 years. The initial study period for the R-01 ended on August 31, 2005. We were fortunate that we were renewed for 2 consecutive 5 additional years at that time as a U-01 which is a cooperative research agreement with NIDDK. Averell

Shaker, MD is our Project Scientist and Edward Doo, MD is our program official at NIDDK. An independent review and data safety monitor board (DSMB) has been appointed by the NIH to oversee the blind study from a safety and efficacy standpoint. Michael R. Lucey, MD, University of Wisconsin is the DSMB chairman.

Time Line of the ALFSG

Initial group organizational meeting DDW	May 12, 1996
Data collection for 2 year retrospective study	July 1, 1996
RO3 grant submitted	October 1, 1996
Grant award announced	May 1, 1997
Actual grant period began	September 1, 1997
Form design, IRB submissions	October/November, 1997
Prospective data collection began	January 1, 1998
Site selection for pilot study	April 1, 1998
FDA FD-R-001661-01 grant submitted	September 1, 1998
Pilot study of NAC treatment began	February 1, 1999
RO3 funding ceased	August 31, 1999
FDA funding began	September 1, 1999
RO1 grant application submitted	October 1, 1999
Pediatric study began	January 1, 2000
RO1 funding began	September 1, 2000
Began larger NAC study (all sites)	September 1, 2000
Ramped up number of adult sites to 23	September 1, 2001
Submitted Competing Continuation	November 1, 2004
RO1 funding ceased	August 31, 2005
UO1 funding began	September 1, 2005
U01 renewal began	September 1, 2010

Grants Contract and Payments

The grants contract specialist at UTSW will negotiate the contract with each site. Each site's budget will be established by their previous year's level of participation with the study group.

A site can begin billing UTSW once the contract is in place. There are several steps involved in the billing process. In the contract you will be assigned a Grants Management Office number (GMO#). While site's accounting/contracts specialists will more than likely be submitting the

invoices for time worked on the study, please make note of the GMO number, in case you need to refer to it in the future. Invoices should go directly from the site's accounting office to the accounting office at UT Southwestern.

Meeting

Brief organizational meetings have taken place and are expected to continue to take place during Digestive Disease Week (DDW) and the American Association for the Study of Liver Diseases (AASLD) fall meetings. There is also an Annual Face to Face meeting that traditionally has occurred during the winter. The Annual Face to Face meeting is a more intensive meeting is includes presentations of topics related to ALF, including an update of the study results, discussion of organizational issues and sub-committees meetings. During the annual meeting, principal investigators and site study coordinators are able to meet and exchange ideas and information in support of the study. Expenses incurred in attending the Annual Face to Face meeting are reimbursed.

Regulatory Requirements

A current Medical License and CV of the site's principal investigator and all sub-investigators involved in the study should be on file at UTSW. In addition, the sites should forward a copy of their Delegation of Authority log, 1572, CLIAs and lab ranges to angela.bowling@utsouthwestern.edu

Institutional Review Boards

Study documents approved by UTSW's Institutional Review Board (IRB) will be forwarded to each site. It is the site's responsibility to submit study documents to their IRB. This includes protocols, consents and continuing reviews and any future amendments. Failure to obtain re-approval of the protocol from their IRB will disqualify a center from participation "until the paperwork is completed or until the protocol is reapproved." The site must submit copies of their IRB approved documents to Angela Bowling at angela.bowling@utsouthwestern.edu.

Confidentiality

Confidentiality regarding patient identities must be maintained at all times. Because of the frequently fatal outcomes observed in acute liver failure, and the possibility of litigation surrounding the occasional case (toxins, drug reactions, etc.), it is imperative that we emphasize that confidentiality is being maintained. The patient numbers will be assigned using a web based program which is part of the electronic data capture system. This assigned number will be unique

throughout the study and for that specific patient; therefore it will not change if an ALI patient becomes ALF. All bio-samples will only be coded by patient number, date of collection and sample type. Please notify Lynn Patterson (pattersl@musc.edu) for a copy of the WebDCU manual.

Consenting Process

Consent may be obtained from the patient if enrolling in the ALI study. Intubated and non-hepatic cognitively impaired subjects may not consent for themselves; therefore, consent must be obtained from next of kin or patient advocate. If it is an ALF case, consent must be obtained from next of kin or patient advocate. After consent is obtained, the person signing consent should be given a photocopy of the signed document. A copy of the consent should be placed in the subject's medical record, and the original copy of the consent must be filed in the study binder. It is not necessary to forward the patients' signed consents to UTSW. It is presumed that the time of admission will be the same as the time that the consent was signed. However, there may be exceptions. For example, it might be possible to obtain the consent in the Emergency Room and wait three or four hours to collect the admission data once the initial laboratory tests are performed and a full physical examination is done

Data Collection Procedures

The following table outlines the schedule for specimen and data collection as outlined in the protocol:

ALFSG Data Collection Schedule version 8

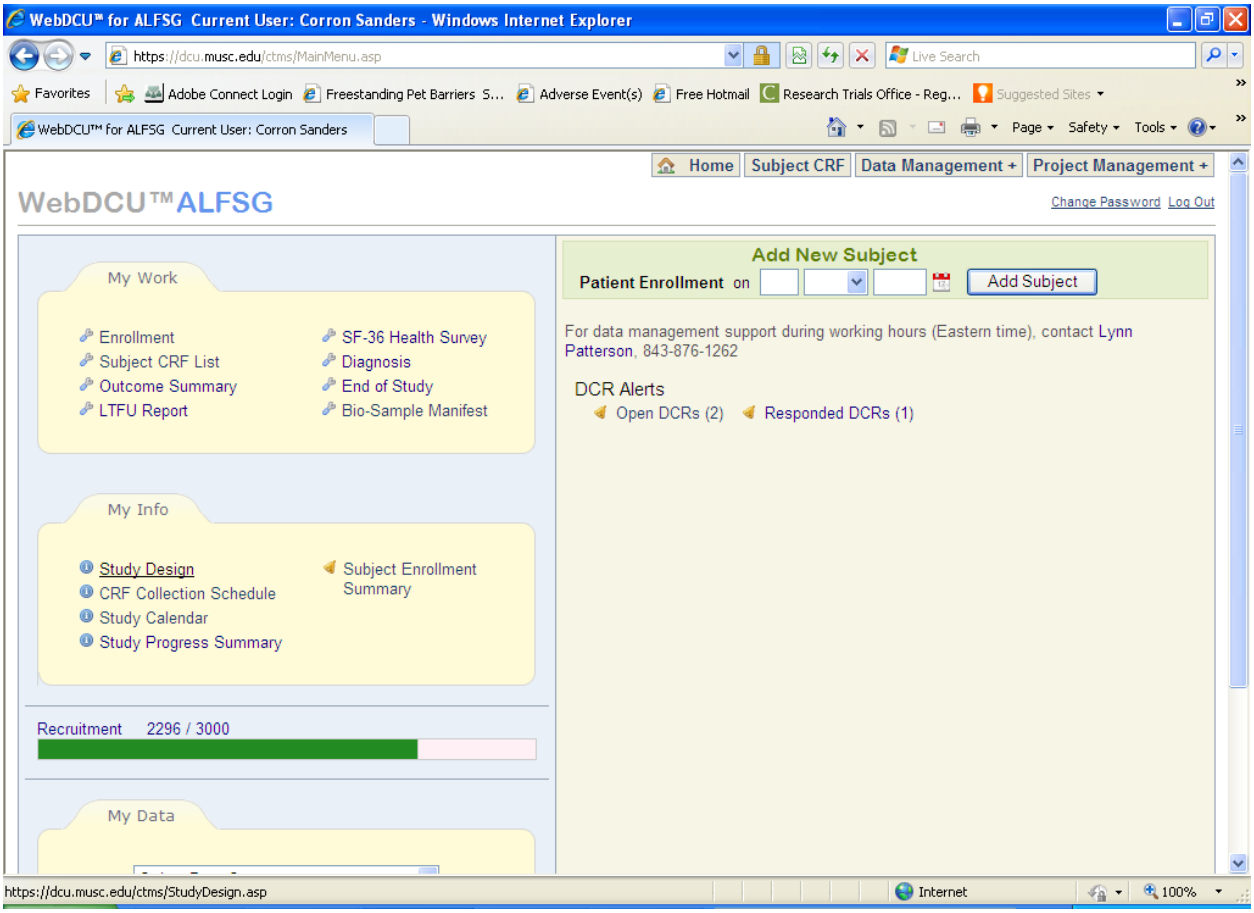
CRF #	CRF Name	Patient Enrollment	ALI							ALF							Long Term FU (ALI/ALF)			End of Study
			Admission Day 1	Inpatient						Admission Day 1	Inpatient						Discharge Summary			
				Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		Month 6 (wk >18-36)	Month 12 (wk 36-72)	
0	Enrollment	X																		
1	ALI Admission		X																	
2	ALF Admission									X										
3	Medical History	X																		
4	Risk Factors and Past Medication	X																		
13	Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
5	Neurological Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
6	O-log		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
7	Imaging, EEG, Biposy	X																		
8	Lab Data		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
29	Serological Exam	X																		
9	Bio-sample Collection Log		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
11	Pre-Study Peak Lab Values	X																		
12	Daily Check Up		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
27	Glasgow Coma Scale									X	X	X	X	X	X	X				
14	Infections		X							X										
15	Transplant Form	X																		
32	Acute Rejection		O							O								O	O	
16	Diagnosis		X							X										
17	Inpatient Summary																X			
33	STFU Outcome																			
28	Outcome Lab Data																XR	X	X	
30	Contact Log																	X	X	
31	LTFU 3 months																			
18	LTFU Part 1 - Outcome																	X	X	
19	LTFU Part 2 - Complications																	X	X	
20	LTFU Part 3 - Current Medication																	X	X	
21	LTFU Part 4 - Substance abuse																	X	X	
22	LTFU Part 5																	X	X	
23	RBANS Test																	X	X	
24	SF-36 Health Survey																	X	X	
25	CDC HRQOL-14																	X	X	
34	21 Day Status	X																		
35	DNA Collection		X							X										
26	End of Study Form																			X

Outcome visit=Week3/Discharge/Transplant, whichever comes first.

Legend: X= Required O = Optional R = Repeatable CRF

Study Flow

The Study Design located on the WebDCU home page provides an outline of the expected study flow for acute liver injury (ALI) admission subjects, subjects who convert from ALI admission subjects to acute liver failure (ALF), and ALF admission subjects:



CONDUCTING STUDY VISITS FOR THE ACUTE LIVER FAILURE STUDY

Admission Visit

Subjects will be admitted to the study once it has been confirmed they meet the eligibility criteria by an investigator on the study team and consent has been obtained from the subject or the subject's next of kin or patient advocate.

ALF Study Eligibility Criteria

Each study patient must have **all three** features to qualify as having ALF (fulminant or sub-fulminant): a liver-related illness which may or may not include jaundice, of less than 26 weeks duration; any alteration in mental status (presumed not due to sedation alone), and coagulopathy

as determined by prothrombin time ≥ 15 sec or an INR ≥1.5. In the analysis of the data, patients will be divided into fulminant (<8weeks illness) and subfulminant (8-26 weeks illness).

ALI Study Eligibility Criteria

There are distinctive illness duration for the acetaminophen cases (<2 weeks illness duration) and for all other cases (<26 weeks). ALI patients will not have alteration in mental status, INR ≥2.0, and for the non-acetaminophen cases an ALT of ≥10x ULN, and Tbili ≥3.0. If an ALI patient develops alteration in mental status once they have been enrolled into the study and have an INR ≥1.5, they will crossed enrolled into the ALF study.

ALI Subjects

ALI subjects consented for specimen collection should have day 1 samples (urine, plasma, serum, and if applicable DNA) and up to 6 more consecutive days of serum collected. If the one time urine, plasma and/or DNA are not collected on ALI study day 1, they may be collected on a subsequent day. Study day 1 is defined as the day of consent. Some subjects may be consented on study day 1, but have their first samples obtained on study day 2. In this case, there will be no study day 1 samples.

If an ALI subject's status worsens and the meet ALF criteria, day 1 samples for ALF should be collected on the day of conversion and then the subject may have 6 more days of samples drawn as an ALF subject. For example: if an ALI subject converts to an ALF subject on study day 4 the subject's specimen/data collection may be day 1 ALI, day 2 ALI, day 3 ALI, day 1 ALF, day 2 ALF, day 3 ALF, day 4 ALF, day 5 ALF, day 6 ALF, and day 7 ALF. A subject may not convert from ALF to ALI.

ALF Subjects

ALF subjects consented for specimen collection should have day 1 samples (urine, plasma, serum, and if applicable DNA) and up to 6 more consecutive days of serum collected. ALF samples should be collected through ALF study day 7, day of transplant, or hospital discharge (whichever comes first). If the one time urine, plasma and/or DNA are not collected on ALF study day 1, they may be collected on a subsequent day. If the subject is initially enrolled into the study as an ALF subject, ALF study day 1 is defined as the day of consent. If a subject was enrolled into the study with ALI but worsens and meets ALF criteria while on study. ALF study day 1 is the

day the subject meets ALF eligibility criteria and the consent is signed by the next of kin or patient advocate. Some subjects may be consented on study day 1, but have their first samples obtained on study day 2. In this case, there will be no day 1 samples.

If a subject regains the capacity to make decisions for themselves, the subject must be informed of their enrollment into the study and asked to continue to participate. If the subject agrees to continue participating, they should sign the consent form and be given a copy of the signed document. If the subject agrees to permit the researchers to use samples previously collected, but does not want to continue to participate, they should be asked to sign the consent form and then sign a letter of withdrawal. If the subject does not want to participate, they should be asked to sign a letter of withdrawal.

Acetaminophen Questionnaire

All subjects enrolled with acetaminophen toxicity should be asked if they would like to participate in the Acetaminophen Overdose Questionnaire sub-study at the time they sign consent. The questionnaire should be administered to the subject prior to hospital discharge or within a few weeks of hospital discharge. The initial questionnaire comprised of 12 items is administered first. It assesses whether or not the case is unintentional or intentional. The respective unintentional or intentional questionnaire is then administered.

ALF /ALI Follow-up Day 21 Visit Procedures and Activities

ALF subjects should be contacted for follow-up at Day 21 by telephone to review their status. The following information should be collected:

- Was the subject contacted? (Yes or No)
- Was a significant other/ subject's family contacted? (Yes or No)
- If the subject was not able to be contacted by telephone, send the subject and/or their surrogate a certified letter requesting they contact the site.
- If the subject did not respond to the certified letter, check the Social Security death file to see if the subject died.
- Check the subject's medical record to see if any record of death or last date of contact.
- Record if subject alive (Yes or No).
- Record if subject transplanted since ALF hospitalization (Yes or No). If yes, record date of transplant.

- Record if subject hospitalized since ALF hospitalization (Yes or No), If yes, record dates of hospitalization and reason for hospitalization.
- If alive, schedule the follow-up month 6 study visit.

Please refer to the Operations Manual for Long-Term Outcomes Of Acute Liver Failure Study Group Patients 2nd edition and Addendum for procedures regarding Follow-up visits at 6 and 12 months.

ALF /ALI Follow-up 6 Month Visit Procedures and Activities

ALF/ALI subjects should be should be seen in the office/clinic for follow-up at Month 6 (+ 1 month). The following information should be collected:

- Obtain vital signs including weight.
- If patient did not show, check the Social Security death file to see if the subject died.

Check the subject's medical record to see if any record of death or last date of contact.

- Record if subject had a liver transplant since ALF hospitalization (Yes or No). If yes, record date of liver transplant.
- Record if subject was hospitalized since ALF hospitalization (Yes or No). If yes, record dates of hospitalization and reason for hospitalization.
- Record medications.
- Record complications since ALF admission.
- If the subject comes back for an office/clinic visit a neuro examination should be completed**.** Administer RBANS, TRAILS, and HRQOL.
- Obtain a comprehensive lab profile (LFT's and electrolytes), complete blood count (CBC) with, and INR on all subjects. Clinical standard of care lab results may be used for these results if they were obtained within window of visit.
- Obtain 10 mL of serum for research repository aliquoting for research purpose and process per lab manual.
- Schedule the follow-up month 12 visit.

ALF /ALI Follow-up 12 Month Visit Procedures and Activities

The follow-up month 12 visit can be conducted via phone/email/chart review or in person clinic visit. It should be performed for both ALF/ALI subjects (-5/+6 months). However, if the patient cannot come into the clinic for the visit, a phone visit or chart review is appropriate.

- Obtain vital signs including weight.

- If patient did not show, check the Social Security death file to see if the subject died.
- Check the subject's medical record to see if any record of death or last date of contact.
- Record if subject had a liver transplant since hospitalization (Yes or No). If yes, record date of liver transplant.
- Record if subject was hospitalized since last contact (Yes or No). If yes, record dates of hospitalization and reason for hospitalization.
- Record medications.
- Record complications since last study contact.
- If the subject comes back for an office/clinic visit a neuro examination should be completed**.** Administer RBANS, TRAILS, and HRQOL.
- Obtain a comprehensive lab profile (LFT's and electrolytes), complete blood count (CBC) with, and INR on all subjects. Clinical standard of care lab results may be used for these results if they were obtained within window of visit.
- Obtain 10 mL of serum for research repository aliquoting for research purpose and process per lab manual.

STUDY COMPLIANCE

There is a great deal of sub procedures within the ALFSG. It is the data coordinating center's goal to maximize adherence to the protocol and minimize non-compliance. Comprehensive training on the study protocol, early review of the data, and routine communications with the sites will be adopted to help minimize protocol violations.

Protocol deviations include, but are not limited to, the following:

- Failure to obtain Informed Consent
- Failure to keep IRB approval up to date

This section of the MOP should describe relevant violations and the reporting process to appropriate parties, including the Principal Investigator at the study site and at the Coordinating Center within 24 hours of occurrence or as soon as they are discovered. The study coordinator should maintain a log of all protocol deviations and should report them routinely to the data coordinating center.

Source Documentation

A source document is any document on which study data are initially recorded. Source documents include laboratory reports, ECG tracings, medical records, standardized test forms, etc. These data are then transcribed to a paper case report form (CRF) or electronic CRF (eCRF) to document study-specific data requirements.

All essential study documents must be retained by the investigator. The following are considered to be part of the participant file documents:

- CRFs
- Data correction forms
- Workbooks
- Source documents (e.g., lab reports, ECG tracings, x-rays, radiology reports, etc.)
- Signed consent forms
- Questionnaires completed by the participant

Retention of Study Documentation

The length of time all study files are to be maintained for seven years after completion of the study. After this time, please contact the data coordinating center on storage of these files.

ECRF COMPLETION INSTRUCTIONS

General Guidelines

These guidelines have been produced as an aid to principal investigators, study coordinators and anyone who will be responsible for the entry of data into the Case Report Form (CRF), also called electronic CRF (eCRF) and in the review of completed CRFs. For this study, the sponsor has elected to use WebDCU, an electronic data capture system (EDC). The Medical University of South Carolina's office of Division of Biostatistics and Epidemiology in the Department of Medicine owns WebDCU.

To obtain access to the WebDCU, please contact WebDCU.

Note: the terms eCRF and CRF are used interchangeable for this study.

Only subjects who are consented will be entered in the WebDCU. Subjects who are not enrolled (screen failures) should be tracked in the screen failure log.

After each visit, enter the data into the appropriate CRF in a timely manner. All required data-entry fields on the CRFs must contain appropriate, complete, and accurate data to minimize the number of subsequent data queries.

Site staff must respond to queries as soon as possible after generation, within three weeks. Clinical source documents must support all data recorded on CRFs. All data must have a separate identifiable source. For most data, the source will be the subject chart or electronic medical record and local laboratory results.

Entry Conventions

- Avoid the use of abbreviations where possible.
- Dates will be displayed DDMMMYYYY (17MAR2013).

    - Whole Dates: Dates that occur during the trial require Day-Month-Year. If any portion of the date is unknown, provide a best estimate if possible. For any estimation, a note to file should be added to the source documents.
    - Partial Dates: None of the date fields allow partial dates.
    - Common Date Errors: Selecting the wrong month, wrong day, or wrong year. Example, the visit occurred on July 11, 2009, but one assessment date is entered as June, 11, 2009. A query may be created.
    - The wrong year is entered. Example, Visit 1 is 12-Nov-2008, Visit 2 is 12-Dec-2008, Visit 3 is 12-Jan-2008, and Visit 4 is 12-Feb-2009. For Visit 3, the year is entered incorrectly and should be 2009, and you will get a rule violation.
    - The date entered is in the future. For example, if today is 12-Feb-2008 and you enter 13-Feb-2008 or 12-Feb-2009, then you will get a rule violation.

    One way to avoid date errors is to review all the CRFs for a visit as soon as you finish entering the visit.

- Record time in the 24-hour clock format

If the time is:	Enter:
Midnight	00:00
9 am	09:00
2 pm	14:00
9:27 pm	21:27

- DO NOT record a value of “0” to indicate a measurement was Not Done. Record “0” only if this is the actual result.
- When rounding: round up at 5 and above and round down at <5. For example, if field requires 1 significant digit, the result 10.5 would round up to 10.6; whereas the result 10.54 would round to 10.5.
- Only trained and authorized site staff can enter or change the data. When answering queries, please be sure to update the CRF first, if needed. Then, your query response should match the update CRF.

Languages

Please complete the CRF in English. Below is a guide to completing the individual forms.

Paper Templates of the eCRF

A blank paper copy of the eCRF page may be found in the WebDCU under the Project Management Tab.

PATIENT ENROLLMENT FORM

Date of Birth: Enter the subject’s birthdate in the following format DDMMMYYYY (17MAR2013).

Date initial hospital. This is the first recorded date of patient being admitted to the hospital for ALF. This might be an outside hospital.

Time admitted: This is the first recorded time of patient being admitted to the hospital.

Hospital transfer: If the patient was transferred from another hospital, indicate the date of transfer to your hospital. If the patient was admitted from home, then this is not a transfer from another hospital. We have not made provision thus far for careful rendering of records from an outlying hospital but this may be important. Let us know if you need to include data from the referring hospital. Provide the date (dd-mmm-yyyy).

Gender: Enter Male or Female

Ethnicity: If the subject self-identifies as HISPANIC/LATINO, enter HISPANIC/LATINO. Otherwise, chose NOT HISPANIC/LATINO.

Race: In general, list one, but you may list more than one. Record the race the subject self-identifies with. If the appropriate race is not listed, enter OTHER and specify the race.

Employment status: Check the box that indicates the patient's current employment with one of the following:

- Employed-full time
- Employed-part time
- Medical disability
- Student
- Homemaker
- Self-employed
- Retired
- Other capacity
- Unemployed
- Unknown

Years of education: This may not be obtained easily. Specify the number of years reported or check unknown.

Marital Status: Check the box that indicates the subject's marital status from the following

- Never married
- Married
- Divorced
- Separated
- Widowed
- Significant other
- Unknown

ADMISSION FORM

Each site will only have access to add patients enrolled at their sites. The Subject Code (4 digits) are automatically generated by the WebDCU system when you add a new subject and new visit. Refer to the WebDCU Manual of Operations regarding adding new subjects and visits.

When a subject converts from ALI to ALF, the ALF data will begin to be entered by populating the ALF admission form under the next visit tab.

ALF Study Eligibility Criteria: Please check the qualifying features for inclusion in the ALF study. Each study patient may or may not have jaundice/illness < 8 weeks, jaundice/illness ≥ 8 weeks and < 26 weeks, previous sedatives, any alteration in mental status (presumed not due to sedation alone), previous fresh frozen plasma (FFP), and INR > 1.5.

ALI Study Eligibility Criteria: Please check off the qualifying features for inclusion in the ALI study. For the acetaminophen cases jaundice/illness < <2 weeks illness duration; for all other cases jaundice/illness <26 weeks. Mark if the subject received previous sedatives, previous FFP, INR ≥2.0, ALT of ≥10x ULN, and Total bilirubin ≥3.0.

Previous Sedatives or Previous FFP: Recording whether at study admission the patient had received sedatives or FFP is important in interpretation of level of consciousness and whether initial serum samples are uncontaminated with plasma from others.

Has patient met eligibility criteria? If no, provide documentation in the comment section that exemption was granted from Dr. Lee. This should be an email.

Date of onset of hepatic coma grade prior to admission **(For ALF Patients only)**: Provide the first date of the respective hepatic coma grade present prior to admission (I-IV) using the day-month- year format (01-Feb-2011).

Date of consent/ admission: For ALI subjects and subjects enrolled initially as ALF, the date of consent/admission should be recorded as the date the initial consent was signed. For subjects who converted from ALI to ALF this will be the date of conversion to ALF.

Time of consent/admission to study: For ALI subjects and subjects enrolled initially as ALF, the time of consent/admission should be recorded as the time the initial consent was signed. Record the time of consent using the 24-hour time scheme rather than the 12-hour notation.
Physical Exam: Enter data using medical chart physical exam.Symptoms of ALF/ALI: Indicate yes or no to the following symptoms of ALI/ALF based upon physical examination data recorded in the medical record and/or study source documents **at the time of enrollment into the study**.

- Peripheral Edema
- Splenomegaly
- Ascites
- Hyper-flexia
- Pupillary Dilatation

MEDICAL HISTORY FORM

History of Present Illness: Provide a brief history of this present episode.

Date of onset of first symptom: Try to obtain an accurate date of onset for the first symptom, usually this will be fatigue or malaise, but other symptoms have been listed separately.

Specific symptoms: Record (Yes or No or unknown) if it was reported that the subject experienced any of the following symptoms prior to or at the time of study enrollment:

- Nausea/vomiting
- Abdominal pain
- Rash
- Headache
- Malaise
- Fever
- Joint pains
- Jaundice

If Jaundice, date of onset: If the subject was jaundice, provide the date if was first reported.

Specify other symptoms: Record any other symptoms of ALF/ALI not previously listed experienced by the subject prior to enrollment.

Previous diseases and illnesses checklist: Please mark all the disease/system categories which are part of the subject's medical history and specify the diagnosis where applicable and known. The categories include:

- Collagen/vascular disease
- Chronic liver disease
- Endocrine/diabetes
- Psychiatric disease
- Neuro/seizure/hypertension
- Heart disease
- Renal disease
- Pulmonary disease
- Substance abuse
- GI disease (gastrointestinal disease)
- HIV/AIDS
- IDU at any time in past (injectable drug use at any time in past)
- Other

If the subject has an extensive medical history, add the diseases/illnesses to the comment section.

Pre-ALI/ALF Karnosfy score**:** Specify the subject's percentile score for the Karnosky level of functioning prior to their initial hospital admission.

%	Criteria
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self. Unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of own needs

50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very sick; hospitalization necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

RISK FACTORS AND PAST MEDICATION USE FORM

IDU: Answer yes or no to whether the subject has the patient used injection drugs in the past six months? If unknown, leave blank and answer query as unknown.

If it is known that the subject used injectable drugs within the past 6 months, specify the drug type use:

- Amphetamines
- Narcotics
- Cocaine
- Other

Alcohol: Record the usual alcohol intake of the subject within the past 6 months:

- None
- 1 drink per week
- 1-2 drinks per week
- 3-6 drinks per week
- 1 drink a day
- 2 drinks a day
- More than 2 drinks per day

(1 drink ETOH is equivalent to: 12 oz or 1 can of beer, 1.5 oz liquor, 5 oz or 1 glass of wine, 12 oz or 1 wine cooler)

Specify the number of weeks using ETOH during the past 6 months. If unknown, leave blank and answer query as unknown.

Medication Use: List all medications used in the last 6 months, including all herbs, or any xenobiotic ingested as a toxin (mushrooms, acetaminophen, vitamins, etc.), anesthetics, over-the-counter (OTC) meds, as well as prescription drugs. Do not include drugs given in for the current hospital admission unless ALF/ALI developed while the patient was hospitalized. Try to be specific with the patient or family members as to quantity, strength, total daily dose, last date ingested, and for how long. When compound drug containing acetaminophen and another agent has been used, please be specific with its "Trade name" and record the dose of acetaminophen taken per day. List the product taken. Try to specify the total dose and the date and time of the ingestion, as well as whether it was a single time point.

Note that we have not included a long list of peculiar features such as environmental exposures, work-related issues, but these may be covered in the comment section. Occupation is suitable for discussion in the comment section, e.g., health care workers should be identified.
Known drug allergies: For items 9-14, record any known drug allergies and any documented allergic reaction.

Pre-study NAC treatment: For items6-8, 15, record any NAC administration prior to enrollment into the study. Record outside hospital NAC treatment as well.

VITAL SIGNS FORM

Pulse: Record pulse as beats/min at the time of enrollment
Systolic Blood Pressure/Diastolic Blood Pressure: Record blood pressure in mm/Hg at the time of enrollment
Respiration: Record respiration in breaths/min at the time of enrollment
Min Temperature: Record the minimum temperature in degrees Celsius during the 24 hour preceding enrollment

Max Temperature: Record the maximum temperature in degrees Celsius during the 24 hours preceding enrollment
Height: Record subject's height in cm
Weight: Record subject's weight in kg at the time of enrollment

NEUROLOGICAL EXAM FORM

Indicate on all study days (including short and long term follow up visits) whether the following neurological symptoms of ALF/ALI based upon physical examination data recorded in the medical record and/or study source documents.

- Asterixis: mark absent or present.
- Pupillary reflexes: mark fixed or reactive.
- Babinski (up-going great toe]: mark absent or present.
- Reflexes-patellar: mark normo-active, hypo-reflexia, or hyper-reflexes.
- Reflexes-biceps: mark normo-active, hypo-reflexia or hyper-reflexes.
- Posturing-decorticate: mark no posturing or posturing.
- Posturing-decerebrate: mark no posturing or posturing.

THE ORIENTATION LOG (O-LOG) FORM

Record the subject's orientation of log (O-Log) responses:

(1) City. What city are you in? If incorrect first answer, give logical cue according to your city location (for example, for Richmond, VA, "capital of Virginia.")
-if incorrect to logical cue, give multiple choices: "are we in Miami, [your city], or Chicago"?
(2) Kind of place. What kind of place are we in? -if incorrect first answer, give logical cue: "this is where sick people go to be admitted."-if incorrect to logical cue, give multiple choices: "railway station, airport, hospital."
(3) Name of hospital. What is the name of this hospital? -if incorrect first answer, make up logical cue for your hospital.-if incorrect to logical cue, give multiple choices: "[your hospital], Georgetown Hospital, Cornell Hospital."
NOTE: Give full credit (6 points) if patient answers both kind of place and hospital name at the same time.

(4) Month. What is the name of this month? -if incorrect first answer, give logical cue: “it’s the month after [___]”.-if incorrect to logical cue, give multiple choices: month before, current month, month after current.
(5) Date. What is the date of this month? -if incorrect first answer, give logical clue: “it’s the day after [___]”.
-if incorrect to logical cue, give multiple choices: date before, date after, current date.

(6) Year. What is the Year? -if incorrect first answer, give logical cue: “it’s the year before [___]”.
-if incorrect to logical cue, give multiple choices: current year, year before, year after.
(7) Day of week. What is the day of the week? -if incorrect first answer, give logical cue: “it’s the day before [___]”.-if incorrect to logical cue, give 3 multiple choices including the correct day of week.
(8) Clock time. What time is it (show clock/watch to patient)? For this question, there are no cues, and patient receives 3 points for correct response or 0 points for incorrect response. A correct response should be within 30 minutes of the actual time.
For details of administering and scoring O-log, see:
(http://www.tbims.org/combi/olog/olograt.html)

IMAGING/EEG/BIOPSY FORM

Report the last conducted CT or MRI of brain and abdomen, ultrasound of the abdomen, EEG, or biopsy data on the eCRF. The CRFs were revised to allow as much clinical detail within the forms. Sites are not required to fax scanned copies of the report but should keep copies in the patient study binder.

Record the results and date of the following diagnostic procedures:

- CT or MR of brain
- CT of abdomen
- Ultrasound of abdomen
- EEG
- Liver biopsy

LAB DATA FORM

These are the basic values that should almost without fail be available on all patients at admission to study: CBC, electrolytes, hepatic studies, arterial blood gasses, and toxin screen, lactate level. Ionized calcium and glucose levels have now been added to the list. Blood for arterial ammonia can be collected at the same time as the arterial blood gases (ABGs). In addition to admission to study, record available lab data for study days two through seven and lab data at study outcome (i.e. at transplant or death). Record the daily lab data. Try to record the lab data at the same time every study day. For lab values, be sure to correctly check the unit of measurement that was used in comparison to the unit of measurement of the eCRF.

Date: Provide the date of lab draw.

Laboratory results should be recorded daily. The results should be reviewed for accuracy. The following Table summarizes the ALF reference range for some of the labs. Lab values with ALF range will generate a warning if the recorded values are outside of these ranges.

BLOOD	**ALF RANGE**	**UNITS**
Hemoglobin	4 - 17	g/dL
Hematocrit		%
WBC	0.5 - 60	1000/mm^3
Differential: PMN		%
Differential: Lympocytes		%
Differential: Eosinophils		%
Differential: Monos		%
Platelet count	20 - 750	1000/mm^3

LIVER	**ALF RANGE**	**UNITS**
Prothrombin time	11 - 99	seconds
INR	05 - 10.0	
ALT	5 - 20,000	IU/L
AST	5 - 20,000	IU/L
ALK phos	30 - 1,000	IU/L
Albumin	0.5 - 5.8	gm/dL
Total protein		gm/dL
Bilirubin	0.1 50	
Glucose		mg/dL
Amylase		IU/L
CK		IU/L
Lipase		IU/L

KIDNEY/ELECTROLYTES	ALF RANGE	UNITS
Creatinine	0.4 – 15	mg/dL
BUN		mg/dL
Na		mmol/L
K		mmol/L
HCO3		mmol/L
Chloride		mmol/L
Phosphate		mg/dL
Magnesium		mEq/L
Total calcium		mg/dL
Ionized calcium		mg/dL
Lactate		mmol/L

ARTERIAL/TOXINS	ALF RANGE	UNITS
pH		
pO_2		mmHg
pCO_2		mmHg
Standard bicarbonate		mEq/L
O2 saturation		%
FiO2		%
Arterial ammonia		
Venous ammonia		
Toxic screen positive (excluding acetaminophen)		
If Toxic screen positive, indicate drug		
Acetaminophen level		

Serological parameters: This includes all the serological tests for viruses, as well as pregnancy.

Miscellaneous: This includes serum autoantibodies, copper studies, α-FP and any other relevant tests performed.

PRE-STUDY PEAK LAB VALUE FORM

In addition to capturing clinical lab data collected during admission to the study, sites are asked to collect data on pre-study values. These values are for values prior to the patients' admission to the study. This may include values from your site or a referring hospital if applicable. This way we can capture any important values prior to study entry. When a subject converts from ALI to ALF, the peak/trough values should be for the ALI and ALF hospitalization respectively.

LAB	ALF RANGE	UNITS
INR	0.5 - 10	
ALT	5 - 20,000	IU/L
AST	5 - 20,000	IU/L
Bilirubin	0.1 - 50	mg/dL
Creatinine	0.4 - 15	Mg/dL

BIO-SAMPLE COLLECTION FORM

This form is completed for those participants who consent to provide biological samples for storage at bio-repositories. Urine, serum, tissue, and plasma specimens will be shipped to the NIDDK Biosample Repository at Fisher Clinical Services. Whole blood specimens for DNA extraction will also be obtained and shipped to UT Southwestern Medical Center for processing for those participants who provide consent. See the bio-samples MOP for specific instructions regarding collecting, storing and shipping samples.

Tissue: Record whether Tissue was collected from the patient, collection date, date shipped to the repository, tissue format (Frozen, Slides, Block), and if there is an available pathology report.

Plasma**:** Record whether plasma was collected from the patient, collection date, collection time, date shipped to the repository. Try to obtain plasma samples on day of admission to study or latest study day 3.

Urine: Record whether urine was collected from the patient, collection date, collection time, date shipped to the repository. Try to obtain plasma samples on day of admission to study or latest study day 3.

Serum*:* Record whether serum was collected (for each study visit) from the patient, collection date, collection time, date shipped to the repository.

DNA COLLECTION FORM

Record whether DNA was collected from the patient, collection date. How many tubes of DNA were collected. DNA can be collected any study day.

Note: When a subject converts to ALI from ALF:

The sample collection protocol begins again. Serum is collected for up to an additional 7 days with a possible total collection days of 14. Plasma and urine samples are collected once again.

DNA only needs to be collected once. **See Biosample Manual of Operation for specific guidelines of collection, processing and shipping biosamples.**

GLASGOW COMA SCALE (GCS) FORM

Coma Grade: Coma grade if this is an ALF case, Register coma grade:

I = any alteration in mentation. This may be highly subjective, and includes agitation, inappropriateness, reversal of sleep pattern, altered calculation or memory.

II = somnolent or obtunded but easily rousable, may demonstrate asterixis.

III = rousable only with difficulty, may mumble a few words or respond to pain with groan or withdrawal.

IV = unresponsive even to deep pain, pupils responsive to light, may have decerebrate posturing.

Coma Grade not evaluable

The Glasgow Coma Scale

The scale comprises three tests: eye, verbal and motor responses. The three values separately as well as their sum are considered. The lowest possible GCS (the sum) is 3 (deep coma or death), while the highest is 15 (fully awake person).

Best eye response (E)

There are 4 grades starting with the most severe:

1. No eye opening
2. Eye opening in response to pain. (Patient responds to pressure on the patient's fingernail bed; if this does not elicit a response, supraorbital and sternal pressure or rub may be used.)
3. Eye opening to speech. (Not to be confused with an awaking of a sleeping person; such patients receive a score of 4, not 3.)
4. Eyes opening spontaneously

Best verbal response (V)

There are 5 grades starting with the most severe:

1. No verbal response
2. Incomprehensible sounds. (Moaning but no words.)
3. Inappropriate words. (Random or exclamatory articulated speech, but no conversational exchange)

4. Confused. (The patient responds to questions coherently but there is some disorientation and confusion.)
5. Oriented. (Patient responds coherently and appropriately to questions such as the patient's name and age, where they are and why, the year, month, etc.)

Best motor response (M)

There are 6 grades starting with the most severe:

1. No motor response
2. Extension to pain (abduction of arm, internal rotation of shoulder, pronation of forearm, extension of wrist, *decerebrate response*)
3. Abnormal flexion to pain (adduction of arm, internal rotation of shoulder, pronation of forearm, flexion of wrist, *decorticate response*)
4. Flexion/Withdrawal to pain (flexion of elbow, supination of forearm, flexion of wrist when supra-orbital pressure applied ; pulls part of body away when nail bed pinched)
5. Localizes to pain. (Purposeful movements towards painful stimuli; e.g., hand crosses mid-line and gets above clavicle when supra-orbital pressure applied.)
6. Obeys commands. (The patient does simple things as asked.)

INFECTIONS FORM

A common complication, this is the simplest method we could devise for tracking and reporting this data.

Culture: Specify source of all positive cultures.

Organism: Specify identified organism if known. Check all that apply.

Antimicrobials used: Please list separately the antibiotics used for prophylaxis of infection and therapy of infection (s). Record outcome of the infection(s).

Hospital course/comments:

TRANSPLANT FORM

Immunosuppression*:* ***(Transplant recipients only)***

We wanted to ask you about the medication you are currently taking (if any) to prevent the rejection of your liver. What medication are you currently taking to prevent rejection of your liver?

Donor Graft #1:

Provide the recipient and donor blood type. Provide the donor age and gender. Also provide the time of the procedure whether cold or warm.

Narrative summary:

We need to capture some basic information about the transplant process itself, when transplants are performed, etc. so that we can provide insight as to outcome based on day of performance, coma grade, etc. This includes Waiting list information, donor graft information, and the type of immunosuppressants that the patient is on. The forms were revised to capture wait-listing time.

ACUTE REJECTION FORM

Complete this form only if the patient had a transplant and acute rejection.

DAILYCHECK UP FORM

The following information will be checked daily by the attending physician or designee staff.

- In ICU
- ICP monitor
- CXR
- Body temperature <36 or > 38
- Heart rate
- High respiratory
- White blood cell count
- SIRS calculated by computer
- Complications
- Treatments
- Specific therapies

ICP MONITOR

- Daily Min value
- Daily Max value
- Type of monitor
- Complications of monitoring

- Primary reason for ICP withdrawal

DIAGNOIS FORM

Diagnosis: The PI or sub-investigator should list the apparent etiology of this episode of acute liver failure or injury as clearly as is known. It is unlikely that there would be two causes, but occasionally there might be (hepatitis B plus acetaminophen, for example). **Uniform guidelines for the different diagnoses criteria are LISTED BELOW. It is important that other diagnoses are truly excluded in those cases said to be indeterminate.**
How final diagnosis established. List the basis for the diagnosis. More than one category may be used, i.e., biopsy plus lab.

Of note, Acetaminophen Overdose:

Acetaminophen Overdose: We wish to track acetaminophen overdoses. In most instances, there is a clear story of either a purposeful overdose with suicidal intent, or an unintentional (accidental) overdose in an attempt to relieve pain.
Acetaminophen overdose: Indicate yes or no if the etiology of the ALI or ALF was an acetaminophen overdose. If unsure, leave blank and answer query.
If yes, specify type: For subjects who developed ALI or ALF associated with acetaminophen overdose, indicate if:

- Suicide attempt
- Unintentional overdose
- Unknown.

If unintentional or unknown, motivation of overdose: If the subject developed ALI or ALF due to acetaminophen toxicity and it was unintentional or unknown overdose, specify if the motivation was MD recommended or self-initiated.

If unintentional, indication for acetaminophen use: If the overdose of acetaminophen was unintentional, specify the reason the subject took the acetaminophen.

ALF/ALI Study Diagnostic Criteria

Specific diagnoses should fulfill the following criteria.

Acetaminophen

History of acetaminophen ingestion (either suspected overdose or chronic ingestion, especially in combination with significant alcohol use)

- Toxic serum acetaminophen level

or

- ALT > 3500 U/L with a history of acetaminophen ingestion irrespective of the acetaminophen level

ALF of Pregnancy

- ALF occurring between 26 weeks gestation and the immediate postpartum period. Liver biopsy c/w diagnosis (ie microsteatosis)
- HELLP syndrome defined ALF occurring between 22 weeks gestation and the immediate postpartum period (> 90% cases) presence of hemolysis, elevated LFTs (transaminases) and low platelets (< 100,000) often associated with hypertension/pre-eclampsia

Autoimmune Hepatitis

- Globulins elevated > 1.5X ULN.
- ANA, ASMA or LKMA positive in titer of at least 1:80.
- Negative serology for viruses associated with acute or chronic hepatitis
- Liver biopsy showing CAH.

Budd-Chiari

- Obstruction of blood flow of the centrilobular veins at any level as shown by: doppler US and angiography
- Liver biopsy c/w diagnosis

Drug-Induced Hepatitis

- Temporal relationship between exposure to suspected drug and onset of ALF (SEE Causality assessment form on eCRF 16 page 3 of 5).
- Exclusion of other causes.

Hepatitis A

- Positive anti-HAV IgM

Hepatitis B

- Positive anti-HBc IgM
- Positive HBsAg.

Delta Hepatitis

- Positive HBsAg.
- Positive anti-HDV
- Positive anti-HBc IgM

Hepatitis C

- Positive anti-HCV (may be absent early in the infection).
- Positive HCV RNA by PCR.

Hepatitis E

- Positive anti-HEV IgM

Mushroom Intoxication

- Temporal relationship between mushroom ingestion and onset of ALF.
- Exclusion of other causes.

Shock/Ischemia

- Development of ALF following documented hypotension.
- Development of ALF in association with a documented low flow state eg severe cardiac failure.
- Exclusion of other causes.

Wilson's Disease

- Serum ceruloplasmin < 20mg/dl
- Elevated serum free copper > 25μg/dl
- Urinary copper excretion > 100 μg/ 24 hours
- Copper concentration in liver biopsy > 250 μg/g of dry weight.

Other Viruses

- HSV: anti-HSV IgM positive and anti-HSV IgG negative and four fold increase between acute and convalescent sera and HSV seen in liver tissue

- EBV: anti-EBV IgM or EBV seen in liver tissue
- CMV: anti-CMV IgM positive and anti-CMV IgG negative and four fold increase between acute and convalescent sera or CMV seen in liver tissue

Indeterminate

Exclusion of all the above diagnoses on the history and serology and other laboratory tests.

OUTCOME SUMMARY FORM

Outcome at time of summary: Summarize in outline form the final outcome for the patient. Confirm if the patient is Alive at end of 3 week study period. If Alive is "No," then complete End of Study Form. If still hospitalized but not transplanted, this should be evident: (alive yes, transplanted no, discharged no).

Narrative summary/Interval history: Provide background information for the case. This will help us when we piece together the data.

Patient Status (For ALI patients only): This field is only for ALI patients at time of summary. Only one field can be "Yes" the other two must be "No."

Last name of reviewing principal investigator: All narrative CRF pages must be reviewed and signed by the study investigator.

OUTCOME LAB DATA FORM

For subjects who discharge, die, or transplant **prior** to Day 7:

At the Outcome visit, please check 'data collected?' as no.

For subjects who discharge, die or transplant **after** Day 7:

At the Outcome visit, please enter the lab data collected prior to discharge, death or transplant, whichever comes first.

At LTFU visit, this form should only be completed if Question 9 on Form 15: Transplant Form is yes. The Data on this form should reflect the labs collected prior to transplant.

21 DAY STATUS FORM

At 21 days post ALI or ALF admission (whichever comes first), what is the vital status of the subject?

FOLLOW UP CONTACT LOG FORM

Data collection method for follow up visit.

Check all that apply: Chart, phone, clinic visit, no data collected

If Phone or Clinic Visit, then the Form is Complete.

Number of attempts made to contact the subject (phone, email, text): If <3, explain in question 7.

Number of attempts made to contact the subject's next of kin (phone, email, text): If <3, explain in question 7.

Certified letter sent?

Certified letters should be sent as needed for the 6 and 12 month visits.

If yes, certified letter returned?

(6 and 12 month visits)

Medical records searched? If 'no', explain in question 7.

SSDI (Social Security Death Index) checked? If 'no', explain in question 7.

To check the SSDI, log onto

rootsweb.com

click on the social security death index section. You can search by the patient's name or by their social security numbers.

If Death is listed in the SSDI, then complete the End of Study Form.

Follow Up Visits

The following forms are completed for the months 6 and12 follow up visits. Imaging/EEG/Biopsy Form, BiosampleCollection Log, Transplant Form, Acute Rejection Form, Outcome Data Form, Contact Log Form, LTFU Part 1-Outcome Form, LTFU Part 2-Complications, LTFU Part 3-Current Medications, LTFU Part 4-Substance Abuse, LTFU part 5, RBANS, SF-36 and CDC HRQOL-14

Please refer to the LTFU manual of operations and procedures.

END OF STUDY FORM Complete this Form only if patient ends the study (i.e. died, withdrew consent or completed 12 month follow up visits).

End of study date: This is the date of the patient's last study visit.

Did the subject terminate the study early?

Yes: Check if the patient completed all visits, including the appropriate follow-up visit(s).

No: If no: Choose primary reason: Indicate just 1, the primary, reason that the patient did not complete the study.

Reference:

Register coma grade:

I - any alteration in mentation. This may be highly subjective, and includes agitation, inappropriateness, reversal of sleep pattern, altered calculation or memory. Asterixis may be absent.

II - somnolent or obtunded but easily rousable, may demonstrate asterixis.

III - rousable only with difficulty, may mumble a few words or respond to pain with groan or withdrawal.

IV - unresponsive even to deep pain, pupils responsive to light, may have decerebrate posturing. Assessment of admission edema, splenomegaly, ascites, hyper-reflexia, pupillary dilatation (>5 mm and hypo- or unresponsive) using only physical examination techniques.

Calculations:

FiO_2 conversions (achieved with a cannula or catheter):

FiO_2 – 20% at room temperature

1L ~ 20% + inspired O_2 0.03 to 0.04 per L (i.e., 3 to 4%)

*thus, 2L ~ 28%

3L ~ 32%

4L ~ 36%

5L ~ 40%

6L ~ 44%

*note: these are approximations

Conversions:

1 in = 2.54 cm

1 lb = 0.4536 kg

1ºF = 1.8xºC + 32

Mean Arterial Pressure (MAP)

$$= \frac{[(2 \times \text{diastolic}) + \text{systolic}]}{3}$$

Abbreviations

A number of people have asked us about some of the abbreviations used in both the admission and outcome forms. Here is a key that should help:

St.BC: Standard bicarbonate

MAP: Mean arterial pressure. This is given by many electronic BP monitors or in those individuals who have an arterial line in situ.

PEEP: Positive end expiratory pressure

PCWP: Pulmonary capillary wedge pressure

NAC: N-acetylcysteine

ELAD: Extra corporeal liver assist device (including BAL – bioartifical liver).