IRB Study Application

1.0 General Information

* Enter the full title of your study:

Functional Assessment in Liver Transplantation

* Enter the study number or study alias

Functional Assessment in LT

* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add Department(s)

2.1 List departments and/or research programs associated with this study

Primary Dept?	Department Name
8	UCSF - 138344 - M_MED-EDUC-CORE

3.0 Assign key study personnel(KSP) access to the study

3.1 * Please add a Principal Investigator for the study:

Jennifer C Lai

Select if applicable

c Department Chair c Resident c Fellow

If the Principal Investigator is a Student, Resident, or Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Kenneth E Covinsky

Other Investigator

Sandy Feng MD

Other Investigator

Laura A Huppert

Other Investigator

Monika A Sarkar

Other Investigator

Norah A Terrault, MD

Co-Principal Investigator

B) Research Support Staff

Stephanie Chau

Research Assistant

Rebecca Halpert

Research Assistant

Selena Z Kuo

Study Coordinator

Adrienne E Lebsack

Study Coordinator

Yara Mohamad

Study Coordinator

Rachel Mustain

Study Coordinator

James Salazar

Study Recruiter

Mariya L Samoylova

Biostatistician

Marie J Sinclair

Study Recruiter

Connie W Wang

Study Coordinator

3.3 Please add a Study Contact:

Jennifer C Lai

Adrienne E Lebsack

Yara Mohamad

Rachel Mustain

Mariya L Samoylova

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Qualifications of Key Study Personnel

4.1 November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements: UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in

conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website. List the study responsibilities and qualifications of any individuals who qualify as Key Study Personnel (KSP) at UCSF and affiliated sites ONLY by clicking the "Add a new row" button. This information is required and your application will be considered incomplete without it.

KSP Name	Description of Study Responsibilities	Qualifications
Lai, Jennifer C	As principal investigator, Dr. Lai will be responsible for all aspects of this study including study design, securing and managing funding, patient recruitment, data analysis, and manuscript preparation.	Dr. Lai has received formal training for outcomes research through the UCSF CTSI to prepare her for being the principle investigator of this study. In addition, she has been the co-PI on a separate ongoing prospective cohort study.
Terrault, Norah A, MD	Dr. Terrault will serve as co-investigator for this project. As a transplant hepatologist, she will advise Dr. Lai on the clinical relevance and feasibility of this project on a population of cirrhotics/liver transplant candidates.	Dr. Terrault has years of experience as a researcher. She has successfully obtained funding, designed studies, analyzed data, and published extensively in the field of liver transplantation.
Dr. Feng, Sandy MD	Dr. Feng will serve as a co-mentor for Dr. Lai throughout this project. As a transplant surgeon, she will advise Dr. Lai on the clinical relevance and feasibility of this project.	Dr. Feng has years of experience as a researcher and mentor. She has successfully obtained funding, designed studies, analyzed data, and published extensively in the field of liver transplantation.
Covinsky, Kenneth E	Dr. Covinsky will serve as a co-mentor for Dr. Lai throughout this project. As a geriatrician with a research focus in functional decline in elderly, he will advise Dr. Lai on the funcation/frailty-related aspects of this project.	Dr. Covinsky has years of experience as a researcher and mentor. He has successfully obtained funding, designed studies, analyzed data, and published extensively in the field of functional decline in aging populations.
Wang, Connie W	Connie will serve as study coordinator. She will help with patient recruitment/enrollment and administrative tasks for the study including making data collection sheets, entering in data, and identifying eligible patients via electronic health record review.	Connie has been fully trained by the principal investigator (Lai) to perform these tasks.
Salazar, James	James will serve as research assistant. He will help with patient recruitment/enrollment.	James has been fully trained by the principal investigator (Lai) to perform these tasks.
Lebsack, Adrienne E	Adrienne will serve as study coordinator. She will help with patient recruitment/enrollment and administrative tasks for the study including making data collection sheets, entering in data, and identifying eligible patients via electronic health record review.	Adrienne has been fully trained by the principal investigator (Lai) to perform these tasks.
Kuo, Selena Z	Selena will serve as research assistant. She will help with patient recruitment/enrollment and administrative tasks for the study including making data collection sheets, entering in data, and identifying eligible patients via electronic health record review.	Selena has been fully trained by the principal investigator (Lai) to perform these tasks.

Samoylova, Mariya L	Mariya will serve as biostatistician. She will be involved with data analysis.	Mariya has been fully trained by the principal investigator (Lai) to perform these tasks.
Mustain, Rachel	Rachel will serve as study coordinator. She will help with patient recruitment/enrollment and administrative tasks for the study including making data collection sheets, entering in data, and identifying eligible patients via electronic health record review.	Rachel has been fully trained by the principal investigator (Lai) to perform these tasks.
Halpert, Rebecca	Rebecca will serve as research assistant. She will help with administrative tasks for the study including making data collection sheets and entering in data.	Rebecca has been fully trained by the principal investigator (Lai) to perform these tasks.
Sarkar, Monika A	Dr. Sarkar will serve as a co-investigator for Dr. Lai throughout this project. As a hepatologist, she will consult with Dr. Lai on the clinical relevance and feasibility of this project, as well as, assist in biomarker sample collection.	Dr. Sarkar has years of experience as a researcher. She has successfully obtained funding, designed studies, analyzed data, and published extensively in the field of hepatology.
Sinclair, Marie J	Marie will serve as research assistant. She will help with patient recruitment/enrollment for the biomarkers sub study.	Marie has been fully trained by the principal investigator (Lai) to perform these tasks.
Mohamad, Yara	Yara will serve as study coordinator. She will help with patient recruitment/enrollment and administrative tasks for the study including making data collection sheets, entering in data, and identifying eligible patients via electronic health record review.	Yara has been fully trained by the principal investigator (Lai) to perform these tasks.

5.0 Initial Screening Questions - Updated 9/13 (Note: You must answer every question on this page to proceed). If you are converting to the new form, check questions 5.4, 5.6, 5.7, 5.8 and 5.10 before saving and continuing to the next section.

5.1 * Application type:

8 Full Committee
m Expedited
m Exempt

5.2 * Risk level (Help Text updated 9/13):

m Minimal risk
8 Greater than minimal risk

5.3 * Subject contact:

8 Yes (including phone, email or web contact)
m No (limited to medical records review, biological specimen analysis, and/or data analysis)

5.4 * Funding (past or present):

8 Funded or will be funded (external sponsor, gift, program or specific internal or departmental funds)
m Unfunded (no specific funds earmarked for this project)
m Unfunded student project

5.5 * The Principal Investigator and/or one or more of the key study personnel has financial interests related to this study:

m Yes 8 No

If Yes, the Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

5.6 * This is an investigator-initiated study:

8 Yes m No

5.7 * This study ONLY involves retrospective records review and/or identifiable biospecimen analysis:

m Yes 8 No

5.8 * This is a clinical trial:

m Yes 8 No

Clinical Trial Registration "NCT" number for this trial:

5.9 * This is a multicenter study:

m Yes 8 No

5.10 * This application involves the study of unapproved or approved drugs, devices, biologics or in vitro diagnostics:

m Yes 8 No

5.11 * This application involves a Humanitarian Use Device:

8 No

m Yes, and it includes a research component

m Yes, and it involves clinical care ONLY

5.12 * This study involves human stem cells (including iPS cells and adult stem cells), gametes or embryos:

8 No

m Yes, and requires CHR and GESCR review

m Yes, and requires GESCR review, but NOT CHR review

5.13 * This is a CIRB study (e.g. the NCI CIRB will be the IRB of record):

m Yes 8 No

5.14 * This application includes a request to rely on another IRB (other than NCI CIRB):

m Yes 8 No

Note: If this request is approved, the CHR will NOT review and approve this study. Another institution will be the IRB of record.

6.0 Funding

6.1 Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor: Note: we require only a P Number OR an A Number for funding coming through UCSF. Please avoid these common errors in funding documentation: DO NOT add the A Number if a P Number was already provided OR update the A Number field when a new funding cycle begins. The IRB does NOT use this information or want these changes made. DO NOT add a grant continuation as a new funding source.

External Sponsor:

	Sponsor Name	Sponsor Type	Funding Through	Contract Type:	UCSF RAS "P	UCSF RAS

					number" or eProposal number	System Award Number ("A" + 6 digits)
—	American College of Gastroenterology	05	UCSF	Grant		A117091

Sponsor Name:	American College of Gastroenterology
Sponsor Type:	05
Sponsor Role	Funding
Grant/Contract Number	
Awardee Institution	UCSF
Is Institution the Primary Grant Holder:	No
if No, then who is the Primary Grantee?	
Contract Type:	Grant
UCSF RAS "P number" or eProposal number	
UCSF RAS System Award Number ("A" + 6 digits)	A117091
Grant Number for Studies Not Funded thru the institution:	
Grant Title:	
Award Recipient: If Award Recipient is not the same as identified on the study.	
Explain Any Significant Discrepancy:	

—	American Federation for Aging Research	07	UCSF	Grant		A124233

Sponsor Name:	American Federation for Aging Research
Sponsor Type:	07
Sponsor Role	Funding
Grant/Contract Number	
Awardee Institution	UCSF
Is Institution the Primary Grant Holder:	No
if No, then who is the Primary Grantee?	
Contract Type:	Grant
UCSF RAS "P number" or eProposal number	
UCSF RAS System Award Number ("A" + 6 digits)	A124233
Grant Number for Studies Not Funded thru the institution:	
Grant Title:	
Award Recipient: If Award Recipient is not the same as identified on the study.	
Explain Any Significant Discrepancy:	

—	NIH Natl Institute on Aging	01	UCSF	Grant		A122052

Sponsor Name:	NIH Natl Institute on Aging
Sponsor Type:	01
Sponsor Role	Funding
Grant/Contract Number	
Awardee Institution	UCSF
Is Institution the Primary Grant Holder:	No
if No, then who is the Primary Grantee?	
Contract Type:	Grant
UCSF RAS "P number" or eProposal number	
UCSF RAS System Award Number ("A" + 6 digits)	A122052
Grant Number for Studies Not Funded thru the institution:	

Grant Title:	
Award Recipient: If Award Recipient is not the same as identified on the study.	
Explain Any Significant Discrepancy:	

Gift, Program, or Internal Funding (check all that apply):

c Funded by gift (specify source below)

R Funded by UCSF or UC-wide program (specify source below)

c Specific departmental funding (specify source below, if applicable)

List the gift, program, or departmental funding source:

Department of Medicine Cohort Expansion Award

6.2 If you tried to add a sponsor in the question above and it was not in the list, follow these steps: If funding has already been awarded or the contract is being processed by the Office of Sponsored Research (OSR) or Industry Contracts Division (ICD), your sponsor is already in the system and the project has an eProposal Proposal or Award number. Check with your department's OSR Staff or ICD Officer to ask how the sponsor is listed in the UC sponsor list and what the Proposal or Award number is. Click here to find your OSR staff and here to find your ICD staff. If your sponsor is not yet in the list, enter it in the box below.

8 Sponsor not in list

Only if your sponsor is not yet in the list, type the sponsor's name:

UCSF Older Americans Independence Center, UCSF Department of Medicine

If the funding is administered by the UCSF Office of Sponsored Research, your study will not receive CHR approval until the sponsor and funding details have been added to your application.

6.3 * This study is currently supported in whole or in part by Federal funding OR has received ANY Federal funding in the past (Help Text updated 9/13):

8 Yes m No

If yes, indicate which portion of your grant you will be attaching:

R The Research Plan, including the Human Subjects Section of your NIH grant or subcontract

c For other federal proposals (contracts or grants), the section of the proposal describing human subjects work

c The section of your progress report if it provides the most current information about your human subjects work

c The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

7.0 Sites

7.1 Institutions (check all that apply):

R UCSF

c China Basin

c Helen Diller Family Comprehensive Cancer Center

c Mission Bay

c Mount Zion

c San Francisco General Hospital (SFGH)

c SF VA Medical Center (SF VAMC)

c Blood Centers of the Pacific (BCP)

c Blood Systems Research Institute (BSRI)

c Fresno (Community Medical Center)

c Gallo

c Gladstone

c Institute on Aging (IOA)

c Jewish Home
c SF Dept of Public Health (DPH)

7.2 Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project (Help Text updated 9/13):

c Other UC Campus
c Other institution
c Other community-based site
c Foreign Country

List the foreign country/ies:

7.3 Check any research programs this study is associated with:

c Cancer Center
c Center for AIDS Prevention Sciences (CAPS)
c Global Health Sciences
c Immune Tolerance Network (ITN)
c Neurosciences Clinical Research Unit (NCRU)
c Osher Center
c Positive Health Program

8.0 Study Design

8.1 * Study design (Help Text updated 9/13):

We propose a prospective cohort study of 2000 patients with cirrhosis who are undergoing Phase 1 evaluation for liver transplantation or who are currently listed for liver transplantation at University of California, San Francisco (UCSF). Each patient will undergo non-invasive frailty measures. They will be followed longitudinally and undergo repeat testing (using the same measures) at 3 month intervals for up to 2 years of follow-up after baseline testing, or until the patient achieves an event (death, removal from the wait-list, or transplant).

8.2 If this is a clinical trial, check the applicable phase(s) (Help Text updated 9/13):

c Phase I
c Phase II
c Phase III
c Phase IV

9.0 Scientific Considerations

9.1 Hypothesis (Help Text updated 9/13):

This study has a hypothesis:

8 Yes m No

If yes, state the hypothesis or hypotheses:

We hypothesize that frailty is associated with liver transplant wait-list mortality and survival after liver transplantation.

9.2 * List the specific aims:

Aim 1: To assess frailty in liver transplant candidates. We will apply various measures of frailty that have been developed for use in elderly patients without chronic liver disease to a patients with cirrhosis awaiting liver transplantation. This will allow us to determine the feasibility of administering each frailty measure and establish expected ranges of the various measures in our population.

Subaim 1: To examine the correlation between frailty measures and MELD score.

Subaim 2: To examine the correlation between frailty measures and sarcopenia, as determined by psoas muscle area on cross-sectional imaging.

Subaim 3: To identify biomarkers of physiologic aging and associate those biomarkers with clinically relevant outcomes such as hospitaliztions and mortality.

Aim 2: To evaluate the association between frailty and wait-list outcomes.

Aim 3: To evaluate the change in frailty over time of patients on the liver transplant wait-list and determine whether the rate of change in frailty is associated with liver transplant outcomes (e.g., wait-list mortality, post-transplant survival).

9.3 Statistical analysis:

Aim 1: Descriptive statistics (e.g., mean, median, range) will be used to summarize each of the frailty measures. Comparisons between groups such as by gender, age, and race, will be made using chi-square or Wilcoxon rank sum tests for categorical or continuous variables, respectively.

Subaim 1: The correlation between frailty measures and MELD score will be assessed with the Pearson correlation coefficient. As there is not a significant clinical difference in wait-list mortality per MELD *point*, MELD score will be categorized for this analysis into 5-point categories (e.g., 20-24, 25-29, etc.).

Subaim 2: The relationship between frailty measures and psoas muscle area will be assessed with the Pearson correlation coefficient.

Subaim 3: Tests of correlation will assosiate biomarkers with clinical tests of physiologic aging such as the Physical Frailty Phenotype, grip strength, walk speed, and timed chair stands. Cox regression modeling will evaluate the association between biomarkers of physiologic aging and hospitalizations/mortality.

Aim 2: The association between each of the frailty measures and the combined endpoint of death or removal for being too sick for transplant will be determined by the Fine-Gray model of competing risks analysis [13, 14]. In this analysis, transplantation will be treated as competing risks, because death on the wait-list cannot logically occur after this event.

Aim 3: Rate of change in frailty will be estimated by dividing the change in frailty by the time interval that has elapsed. The association between change in frailty measures and the combined endpoint of death or removal for being too sick for transplant will be determined by the Fine-Gray model of competing risks analysis (as in Aim 2).

9.4 If this study has undergone scientific or scholarly review, please indicate which entity performed the review:

c Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)

c CTSI Clinical Research Center (CRC) advisory committee

c Departmental scientific review

c Other:

Specify Other:

10.0 Background

10.1 Background:

Every year, one in five patients on the liver transplant wait-list in the United States will die or become too sick while awaiting transplantation (ref: UNOS/OPTN). Although it is widely believed that the shortage of donor livers relative to the need has resulted in these deaths, we recently reported that 86% of those who died or

were removed from the wait-list received at least one liver offer prior to their wait-list event [1], suggesting that increasing donor supply would not substantially reduce wait-list mortality. Furthermore, while all candidates are prioritized for liver transplant by their risk of wait-list mortality as predicted by the objective Model for End-Stage Liver Disease (MELD) score [2], 60% of these patients had a MELD score >17, the cut-off above which transplantation has been shown to provide significant survival benefit over remaining on the wait-list [3]. This suggests that there are factors other than the MELD score that transplant clinicians are using to allocate livers.

One of these factors is the transplant clinician's judgment of the patient's general state of frailty, which describes a *vulnerability* to stresses while on the wait-list combined with *suitability* for transplant surgery. Otherwise known as the "eyeball test", this assessment is made, consciously or subconsciously, each time the transplant clinician sees the patient. The application of the eyeball test to liver allocation decisions may be justified, as there are likely aspects of this test that accurately predict wait-list and post-transplant outcomes. However, it is subjective and may differ from one clinician to another. In addition, there may be components of assessment that falsely identify outcomes. Less charitably, this assessment may incorporate factors which may not be appropriate for liver allocation, including sex, race, and socioeconomic status.

In order to ensure the equity of the liver allocation process, it is paramount to create objective, scientifically validated markers of frailty in patients with end-stage liver disease that accurately predict their outcomes. Many measures, including the Frailty Score [4], Clinical Frailty Scale [5], and the Short Physical Performance Battery [6], have been developed to assess this clinical state in elderly patients, but none have been applied to patients with cirrhosis, a population at increased risk for accelerated functional decline. In addition, given the aging liver transplant population [7], differentiating *functional* age from *chronological* age is becoming increasingly more important.

The objectives of this prospective cohort study are to assess frailty in patients with cirrhosis awaiting liver transplantation and to evaluate the association between frailty, change in frailty, and liver transplant outcomes (e.g., wait-list mortality, post-transplant survival). We conceptualize frailty as the transitional clinical state in the dynamic progression from functional well-being to functional decline [8].

10.2 Preliminary studies:

Background: Decisions regarding liver offers must balance the probability of a better offer with WL mortality risk. We examine WL deaths and offer quality. **Methods**: We examined non-Status 1, adult, LT WL candidates from 2/1/05-1/31/10 (after Share 15) who died/were too sick for LT and received 1 offer (n=9,822) and those who had deceased donor (DD) LT (n=24,842). Only offers of ultimately transplanted livers were studied. A *modified* donor risk index (mDRI) excluded split, cold ischemia time, and share region. Offers with mDRI 50%ile of DDLT livers from donors who were not national, HCV(+), CDC high-risk, or DCD were grouped as higher quality. **Results**: Of the dead/too sick, 86% received 1 offer. Compared to DDLT, the dead/too sick were more likely to be female (38 vs 31%), have portal hypertension (50 vs 44%), and be listed in high LT-MELD donation service areas (48 vs 31%), but less likely to have hepatocellular carcinoma (3 vs 24%) [p .001 for all]. Although the dead/too sick received a greater % of CDC high-risk, national, and HCV(+) donor offers (p< .001 for all), 68% received 1 higher quality offer (Fig); 89% of these higher quality offers were nevertheless refused for donor-related reasons. Fig shows list and last offer LT-MELD. The median time from last offer to death/removal by respective LT-MELD groups was 41, 38, 20, 17, and 7 days (test of trend p< 0.001). **Conclusions**: The vast majority (86%) of WL candidates who died/were too sick received 1 liver offer prior to death/removal. Over a 5-year period, 5,744 patients died/became too sick despite receiving *higher quality* offers. This suggests that availability of DD livers may not reduce WL mortality, but whether these livers *should* be bypassing patients at a higher priority than the eventual recipients remains uncertain.

10.3 References:

References

1. Lai JC, Feng S, Terrault NA, Roberts JP. Liver offers on the liver transplant wait-list (abstract). Hepatology2011.

2. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-70.

3. Merion RM, Wolfe RA, Dykstra DM, Leichtman AB, Gillespie B, Held PJ. Longitudinal assessment of mortality risk among candidates for liver transplantation. Liver Transpl 2003;9:12-8.

4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.

5. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-95.

6. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85-94.

7. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. Am J Transplant2010;10:1003-19.

8. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process. Gerontology 2009;55:539-49.

9. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-6.

10. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. Arch Phys Med Rehabil 1986;67:387-9.

11. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. JAMA 1963;185:914-9.

12. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-86.

13. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk.J Amer Stat Assoc1999;94:496-509.

14. Kim WR, Therneau TM, Benson JT, et al. Deaths on the liver transplant waiting list: an analysis of competing risks. Hepatology 2006;43:345-51.

15. Schiefke I, Fach A, Wiedmann M, et al. Reduced bone mineral density and altered bone turnover markers in patients with non-cirrhotic chronic hepatitis B or C infection. World J Gastroenterol 2005;11:1843-7.

If you have a separate bibliography, attach it to the submission with your other study documents.

11.0 Sample Size and Eligibility

11.1 Number of subjects that will be enrolled at UCSF and affiliated institutions:

1600

11.2 Total number of subjects that will be enrolled at all sites (Help Text updated 9/13):

2600

11.3 Estimated number of people that you will need to consent and screen here (but not necessarily enroll) to get the needed subjects:

2700

11.4 Explain how and why the number of subjects was chosen (Help Text updated 9/13):

Over the course of three years, we have recruited about 200 new patients annually. Our current funding will be availble through 2019 and therefore we believe that it is likely that we'll recruit about 800 more patients locally over the next four years. We also plan to expand nationally and collaborate with future partner sites; we would like to reflect this explansion in our total target enrollment goals,

11.5 * Eligible age range(s):

c 0-6 years
c 7-12 years
c 13-17 years
R 18+ years

11.6 Inclusion criteria:

All patients >=18 years old, either inpatient or outpatient, who are listed for liver transplantation at UCSF or who are undergoing Phase 1 evaluation for liver transplantation are eligible to apply. In addition, we will also recruit inpatients >=18 years old who have undergone liver transplantation during that hospitalization for enrollment in this study.

11.7 Exclusion criteria:

Patients who do not speak English and who do not have an interpreter in clinic will be excluded. In addition, patients who have a physical impairment that prevents them from completing the Numbers Connection Test portion of our assessment without assistance will also be excluded.

11.8 There are inclusion or exclusion criteria based on gender, race or ethnicity:

m Yes 8 No

If yes, please explain the nature and rationale for the restrictions:

12.0 Other Approvals and Registrations

12.1 * Do any study activities take place on patient care units:

m Yes 8 No

If Yes, attach a letter of support for the study from the involved patient care manager(s).

12.2 * Does your protocol involve any radiation exposure to patients/subjects? The UCSF Radiation Safety Committee requires review of your protocol if it includes administration of radiation as part of standard of care OR research exposures:

m Yes 8 No

12.3 * This study may generate genetic data that may be broadly shared (e.g. submitted to NIH for Genome-Wide Association Studies (GWAS) in dbGaP, TCGA, etc):

m Yes 8 No

12.4 * This study involves administration of vaccines produced using recombinant DNA technologies to human subjects:

m Yes 8 No

12.5 * This study involves human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to CHR approval):

m Yes 8 No

12.6 This study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

c Institutional Biological Safety Committee (IBC)

Specify BUA #:

c Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

c Radiation Safety Committee

Specify RUA #:

c Radioactive Drug Research Committee (RDRC)

Specify RDRC #:

c Controlled Substances

13.0 Procedures

13.1 * Procedures/Methods (Help Text updated 9/13) For clinical research list all study procedures, test and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the Methods:

Patients will be asked to perform the following study procedures:

1) Assessment for hepatic encephalopathy using the Numbers Connection Test. This test requires the patient to connect numbers in sequence that are scattered at random on a piece of paper.

2) Measures of frailty were selected to capture the multi-dimensional aspects of frailty including functional status and physiologic reserve:

Frailty Score: shrinking (patient interview), weakness (test of grip strength), exhaustion (patient -
(interview), slowness (patient interview), low activity (patient interview

Short Physical Performance Battery: repeated chair stands, balance testing with feet togheter, 8-foot -
walk

Get-up-and-go test: patient will be asked to stand up from seated position, walk 15 feet turn around and -
walk back to the chair, and sit down

(Katz Index of Activities of Daily Living (patient interview -

(Lawton-Brody Instrumental Activities of Daily Living (patient interview -

3) Laboratory tests will all be obtained from the medical record: creatinine, total bilirubin, international normalized ratio for prothrombin time, sodium, albumin. All of these tests are necessary for listing for liver transplantation. For outpatients, these labs are drawn as part of standard of care, as they are necessary for continued listing for liver transplantation. For inpatients, these labs are routinely drawn on a daily basis for continued listing for liver transplantation.

4) Radiology images (computed tomography and magnetic resonance imaging) will be obtained from the medical record. For outpatients, these scans are routinely performed for hepatocellular carcinoma surveliance. For inpatients, these scans are commonly obtained during hospitalization as part of the work-up for diagnosis or prior to surgery for liver transplantation.

5) Blood draw, urine and stool samples 1000 patients will be consented to undergo one single blood draw of 2 tablespoons of blood and provide a urine and stool sample (about 5ml each or 1 teaspoon each), at the time of consent. If they agree to participate in the long-term specimen storage in the Biorepository specimen bank, then they will have an additional 1 tablespoon drawn during the same venipuncture. Their performance-based mreasure of physiolocia aging (outlined above) will also be obtained at day of consent for this portion of the study and blood draw.

6) Resilience Questions will be asked using a 10 question form to measure patient's degree of resilience.

7) Health Related Quality of Life will be assessed through the Chronic Liver Disease Questionnaire (CLDQ).

8) Adipose, muscle, liver tissue, and blood will be collected during the liver transplant surgery.

- 2X2 cm of muscle tissue will be collected by the surgeon during the liver transplant surgery from the rectus

muscle in the abdomen.
- 2-3 cm³ of adipose tissue will be collected by the surgeon during the liver transplant surgery from the subcutaneous and visceral adipose tissue of the abdomen.
- 4 cm³ of liver tissue will be collected by the surgeon during the liver transplant surgery.
- 4 tablespoon of blood (60ml) will be collected during the liver transplant surgery.

If you have a procedure table, attach it to the submission with your other study documents.

13.2 Interviews, questionnaires, and/or surveys will be administered or focus groups will be conducted:

8 Yes m No

List any standard instruments used for this study:

1) The Frailty Score includes a measure of exhaustion based on the Center for Epidemiologic Studies Depression Scale.
2) Katz Index of Activities of Daily Living
3) Lawton-Brody Instrumental Activities of Daily Living
4) The Physical Activity Scale for the Elderly (PASE) - this consists of 10 questions regarding the patient's physical activities over the last 3 months.
5) Connor-Davidson Resilience Scale 10 (CD-RISC-10)
6) Chronic Liver Disease Questionnaire (CLDQ)

Attach any non-standard instruments at the end of the application.

13.3 Conduct of study procedures or tests off-site by non-UCSF personnel:

m Yes 8 No

If yes, explain:

13.4 Sharing of experimental research test results with subjects or their care providers:

m Yes 8 No

If yes, explain:

13.5 * Specimen collection for future research and/or specimen repository/bank administration:

8 Yes m No

13.6 Time commitment (per visit and in total):

All patients will be asked to complete basic frailty measures: Fried Frailty score, short physical performance battery, Katz activities of daily living, and instrumental activities of daily living. These 4 procedures take no more than 15 minutes to complete. Patients will be asked to complete the Chronic Liver Disease Questionnaire which takes no more than 10 minutes to complete.

Patients will then be followed longitudinally for up to 2 years from baseline testing and be asked to perform repeated measures of testing at their regular hepatology clinic visit every 3 months +/- 4 weeks (patients listed for liver transplantation are followed every 3 months). In cases where a patient does not have a clinic visit, they will be contacted by the study coordinator to set up a visit at UCSF Parnassus campus for frailty testing.

In the subgroup of patients who consent to the blood draw, urine and stool collection, all study procedures (one single blood draw) will take no more than 15 minutes. This blood draw and sample collection will only be performed or collected once.

In the subgroup of patients who consent to the adipose, muscle, liver tissue, and blood collection during liver transplant, all study procedures will take place only during the liver transplant surgery and through sites/tubes are already used for the surgery.

13.7 Locations:

UCSF Moffitt Hospital and Ambulatory Care Clinics

13.8 Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants:

Only appropriately trained staff will administer the tests.

Blood sampling will be performed by licensed personnel: a UCSF phlebotomist (if the patient is undergoing a blood draw for clinical purposes on the same day) or a licensed MD or nurse practitioner.

Adipose, muscle, liver tissue collection during liver transplant will be performed by the same surgeon who is performing the liver transplant.

Blood sampling during the liver transplant will be performed by licensed personnel: a UCSF phlebotomist (if the patient is undergoing a blood draw for the liver transplant surgery) or a licensed MD or nurse practitioner.

14.0 Specimen Collection for Future Research and/or Specimen Repository/Bank Administration

14.1 Specimens are (check all that apply):

R Surplus clinical specimens from a diagnostic or therapeutic procedure
R Specimens collected for research purposes only
c Other

If Other, explain:

14.2 Types of specimens:

R Blood
R Tissue (describe below):
c Existing/archival materials (name source below): --
R Other (describe below):

Describe and/or name source:

Adipose, muscle, and liver tissue during the liver transplant surgery.
urine and stool

14.3 Consent will be obtained via:

R Separate specimen banking consent form
c Specimen banking section within a main research study consent form
c Surgical consent form with tissue donation brochure

14.4 Specimens will ultimately be stored (check all that apply):

UCSF

R UCSF repository/bank being established under this protocol

c Existing UCSF specimen repository/bank with CHR approval

Provide the name of the bank and CHR approval number (if not being banked at UCSF under this protocol):

Outside Entity

c Cooperative group bank
c NIH
c Other university
c Industry sponsor
c Other

Specify to what institution, cooperative group or company specimens will be transferred:

14.5 Direct identifiers will be sent with specimens or shared with other researchers and/or outside entities:

m Yes
8 No
m N/A - Specimens will not be shared with others

If Yes, which identifiers will be sent with specimens:

c Name
c Date of birth
c Social Security number
c Medical record number
c Address
c Phone number
c Email address
c Other dates (surgery date, clinic visit dates, etc.)

If Yes, provide a justification for sending direct identifiers with the specimens:

15.0 Establishing a Specimen Repository/Bank at UCSF

15.1 The repository/bank is physically located at (list the address and room number for all locations):

S-357

15.2 Methods for maintaining confidentiality:

c Samples are completely de-identified before being added to the bank/repository. There is no way to link the specimens back to the subjects.

R Samples are coded and researchers are able to link the specimens to specific subjects. However, future recipients will not receive direct identifiers with the specimens.

c Samples are stored with direct identifiers in the repository. However, future recipients will not receive direct identifiers with the specimens.

c Samples are coded and/or kept with direct identifiers in the repository. The bank/repository may release identifiers with specimens to researchers under special circumstances with prior IRB approval.

Explain under what circumstances identifiers may be released:

15.3 If the repository/bank maintains the identifiers, list the identifiers that will be maintained with the specimens:

c Name
c Date of birth
c Social Security number
c Medical record number
c Address
c Phone number
c Email address
c Other dates (dates of surgery, visit dates)

15.4 Clinical follow-up data will be linked to specimens:

8 Yes m No

If Yes, provide duration of follow-up or indefinitely:

indefinitely

15.5 There is a formal specimen utilization review process:

m Yes 8 No

If Yes, describe the process:

15.6 Specimens banked at UCSF may be made available to (check all that apply):

R UCSF researchers
c Non-UCSF researchers
c Industry

16.0 Alternatives

16.1 Study drug or treatment is available off-study:

m Yes
m No
8 Not applicable

16.2 * Is there a standard of care (SOC) or usual care that would be offered to prospective subjects at UCSF (or the study site) if they did not participate:

m Yes 8 No

If yes, describe the SOC or usual care that patients would receive if they choose not to participate:

16.3 Describe other alternatives to study participation that are available to prospective subjects:

Patients may elect not to participate in this study

18.0 Data and Safety Monitoring Plan

18.1 Describe the plan for monitoring data and safety (Help Text updated 9/13):

Study progress, interim and total adverse events, and unanticipated problems involving risk to subjects will be reviewed twice a year by two independent individuals in the transplant community. Dr. Bilal Hameed (transplant hepatologist) and Dr. John Roberts (abdominal transplant surgeon) were selected based on their expertise in both the clinical and research aspects of transplant hepatology and transplant surgery, respectively. Concerns addressed from the reviews will be communicated to the Committee on Human Resources and/or federal agencies as appropriate.

18.2 This study requires a Data and Safety Monitoring Board:

8 Yes
m No or not sure

If yes, press SAVE and CONTINUE to move to the next section of the application.

18.3 If No, provide rationale:

m Social/Behavioral research

m Phase I trial
m Treatment IND/Compassionate Use Trial
m Other (explain below)

If Other, explain:

19.0 Data and Safety Monitoring Board

19.1 Provide details from the Data and Safety Monitoring Board's charter, including meeting frequency, and affiliations and qualifications of members:

Study progress, interim and total adverse events, and unanticipated problems involving risk to subjects will be reviewed twice a year by two independent individuals in the transplant community. Dr. Bilal Hameed (transplant hepatologist) and Dr. John Roberts (abdominal transplant surgeon) were selected based on their expertise in both the clinical and research aspects of transplant hepatology and transplant surgery, respectively. Concerns addressed from the reviews will be communicated to the Committee on Human Resources and/or federal agencies as appropriate.

19.2 All of the members of the Data and Safety Monitoring Board are independent of the sponsor:

8 Yes m No

20.0 Confidentiality and Privacy

20.1 Plans for maintaining privacy in the research setting:

Strict measures, including password-protection of all data and limitation of access to all data to only study personnel, will be taken to minimize the risk of privacy breach.

20.2 Possible consequences to subjects resulting from a loss of privacy:

There may be social stigma associated with frailty, in which case breach of privacy may cause harm to the patient based on social stigma. Currently, there are no explicit criteria to deny patients liver transplantation based on frailty status, but breach of privacy regarding this information may theoretically be used by insurance companies to deny them liver transplantation.

20.3 Study data are:

c Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
R Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
c Added to the hospital or clinical medical record
c Created or collected as part of health care
c Used to make health care decisions
R Obtained from the subject, including interviews, questionnaires
c Obtained from a foreign country or countries only
c Obtained from records open to the public
R Obtained from existing research records
c None of the above

If derived from a medical record, identify source:

APEX, TITUS (UCSF transplant database)

20.4 Identifiers may be included in research records:

8 Yes m No

If yes, check all the identifiers that may be included:

R Names
R Dates
c Postal addresses
R Phone numbers
c Fax numbers
c Email addresses
c Social Security Numbers*
R Medical record numbers
c Health plan numbers
c Account numbers
c License or certificate numbers
c Vehicle ID numbers
c Device identifiers or serial numbers
c Web URLs
c IP address numbers
c Biometric identifiers
c Facial photos or other identifiable images
c Any other unique identifier

* Required for studies conducted at the VAMC

20.5 Identifiable information might be disclosed as part of study activities:

m Yes 8 No

If yes, indicate to whom identifiable information may be disclosed:

c The subject's medical record
c The study sponsor
c Collaborators
c The US Food & Drug Administration (FDA)
c Others (specify below)
c A Foreign Country or Countries (specify below)

If Others, specify:

20.6 Indicate how data are kept secure and protected from improper use and disclosure (check all that apply):
NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

c Data are stored securely in My Research
c Data are coded; data key is destroyed at end of study
R Data are coded; data key is kept separately and securely
c Data are kept in a locked file cabinet
R Data are kept in a locked office or suite
R Electronic data are protected with a password
R Data are stored on a secure network
R Data are collected/stored using REDCap or REDCap Survey
c Data are securely stored in OnCore

20.7 Additional measures to assure confidentiality and protect identifiers from improper use and disclosure, if any:

20.8 This study may collect information that State or Federal law requires to be reported to other officials or ethically requires action:

m Yes 8 No

Explain:

20.9 This study will be issued a Certificate of Confidentiality:

m Yes 8 No

21.0 Subjects

21.1 Check all types of subjects that may be enrolled:

R Inpatients
R Outpatients
c Healthy volunteers
c Staff of UCSF or affiliated institutions

21.2 Additional vulnerable populations:

c Children
c Subjects unable to consent for themselves
c Subjects unable to consent for themselves (emergency setting)
c Subjects with diminished capacity to consent
c Subjects unable to read, speak or understand English
c Pregnant women
c Fetuses
c Neonates
c Prisoners
c Economically or educationally disadvantaged persons
c Investigators' staff
c Students

Explain why it is appropriate to include the types of subjects checked above in this particular study:

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

22.0 Recruitment

22.1 * Methods (check all that apply):

R Study investigators (and/or affiliated nurses or staff) recruit their own patients directly in person or by phone.

c Study investigators recruit their own patients by letter. Attach the letter for review.

c Study investigators send a "Dear Doctor" letter to colleagues asking for referrals of eligible patients. If interested, the patient will contact the PI or the PI may directly recruit the patients (with documented permission from the patient). Investigators may give the referring physicians a study information sheet for the patients.

c Study investigators provide their colleagues with a "Dear Patient" letter describing the study. This letter can be signed by the treating physicians and would inform the patients how to contact the study investigators. The study investigators may not have access to patient names and addresses for mailing

c Advertisements, notices, and/or media used to recruit subjects. Interested subjects initiate contact with study investigators. Attach ads, notices, or media text for review. In section below, please explain where ads will be posted.

R Study investigators identify prospective subjects through chart review. (Study investigators request a Waiver of Authorization for recruitment purposes.)

c Large-scale epidemiological studies and/or population-based studies: Prospective subjects are identified through a registry or medical records and contacted by someone other than their personal physician. (Study investigators request a Waiver of Authorization for recruitment purposes.)

c Direct contact of potential subjects who have previously given consent to be contacted for participation in research. Clinic or program develops a CHR-approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form for another CHR-approved study.

c Study investigators list the study on the School of Medicine list of UCSF Clinical Trials website or a similarly managed site. Interested subjects initiate contact with investigators.

c Study investigators recruit potential subjects who are unknown to them through methods such as snowball sampling, direct approach, use of social networks, and random digit dialing.

c Other

If Other, explain:

22.2 * How, when, and by whom eligibility will be determined:

For inpatients, eligibility will be determined during their hospitalization to UCSF Moffitt Hospital. For outpatients, eligibility will be determined either during the clinic visit or through a pre-screening process involving chart review of patients scheduled for an outpatient visit in the UCSF Liver Transplant Clinics. The PI, Co-PI, or study coordinator will determine eligibility.

22.3 * How, when, where and by whom potential subjects will be approached:

Inpatients will be approached during their hospitalization. Outpatients will be approached during their clinic visit. Both inpatients and outpatients will be approached by the PI, Co-PI, or study coordinator.

22.4 * Protected health information (PHI) will be accessed prior to obtaining consent:

8 Yes m No

23.0 Waiver of Consent/Authorization for Recruitment Purposes This section is required when study investigators (and/or affiliated nurses or staff) recruit their own patients directly.

23.1 * Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified:

8 Yes

If no, a waiver of consent/authorization is NOT needed.

23.2 * A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

8 Yes

If no, a waiver of authorization can NOT be granted.

23.3 * Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

8 Yes

If no, a waiver of authorization can NOT be granted.

23.4 * Check all the identifiers that will be collected prior to obtaining informed consent:

R Names
R Dates
c Postal addresses
c Phone numbers
c Fax numbers
c Email addresses
c Social Security Numbers*
R Medical record numbers
c Health plan numbers
c Account numbers
c License or certificate numbers
c Vehicle ID numbers
c Device identifiers or serial numbers
c Web URLs
c IP address numbers

c Biometric identifiers
c Facial photos or other identifiable images
c Any other unique identifier
c None

Note: HIPAA rules require that you collect the minimum necessary.

23.5 * Describe any health information that will be collected prior to obtaining informed consent:

Patient names and medical record numbers, laboratory data (to calculate current MELD score), information regarding listing status (active, with or without MELD exception points) will be obtained prior to obtaining information consent.

Note: HIPAA requires that you collect the minimum necessary.

23.6 * Describe your plan to destroy the identifiers at the earliest opportunity consistent with the research or provide a health or research justification for retaining the identifiers, or indicate and explain that retention is required by law:

Patient identifiers will be destroyed at the earliest opportunity once the study has been completed and the information is no longer necessary to follow and study the patients. Patient identification information will be deleted immediately if they decline to participate in the study.

24.0 Informed Consent

24.1 * Methods (check all that apply):

R Signed consent will be obtained from subjects and/or parents (if subjects are minors)
c Verbal consent will be obtained from subjects using an information sheet or script
c Electronic consent will be obtained from subjects via the web or email
c Implied consent will be obtained via mail, the web or email
c Signed consent will be obtained from surrogates
c Emergency waiver of consent is being requested for subjects unable to provide consent
c Informed consent will not be obtained

24.2 * Process for obtaining informed consent:

Informed consent will be obtained on the phone prior to the clinic visit upon pre-screening or in person at the clinic visit (for outpatients) or in the hospital (for inpatients).

24.3 * How investigators will make sure subjects understand the information provided to them:

Trained study personnel will explain the study in detail to the patients and verify that they understand their risks, benefits, and alternatives to participating prior to signing the informed consent form.

25.0 Financial Considerations

25.1 Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

c Subjects will not be paid
c Cash
c Check
c Debit card
R Gift card
c Reimbursement for parking and other expenses

R Other:

Specify Other:

Patients who have undergone functional status testing may be offered a one hour parking voucher and/or a $5 Starbucks or Target gift card. Subjects who consent to the blood draw will be offered a $5 gift card at the time of their blood draw.

25.2 Describe the schedule and amounts of payments, including the total subjects can receive for completing the study. If deviating from recommendations in Subject Payment Guidelines, include specific justification below.

Patients who have undergone functional status testing may be offered a one hour parking voucher and/or a $5 Starbucks or $5 Target gift card. These patients may be offered this after completion of the assessments.

Subjects who undergo an outpatient blood draw will be offered a $5 gift card.

25.3 Costs to Subjects: Will subjects or their insurance be charged for any study procedures?

m Yes 8 No

If yes, describe those costs below, and compare subjects' costs to the costs associated with alternative care off-study. Finally, explain why it is appropriate to charge those costs to the subjects.

26.0 CTSI Screening Questions

26.1 * This study will be carried out at one of the UCSF Clinical Research Services (CRS) centers or will utilize CRS services. CRS centers are at the following sites: SFGH Clinical Research Center Moffitt Adult Clinical Research Center Moffitt Hospital Pediatrics & NCRC Mount Zion Hospital Clinical Research Center Tenderloin Center CHORI Children's Hospital Pediatrics & Adult Clinical Research Center Kaiser Oakland Research Unit SF VA Medical Center Clinical Research Unit Please note: Effective 3/1/14, the CRS form will no longer be completed and submitted in iRIS. The CRS budget request form can be found at: https://accelerate.ucsf.edu/files/crs/BudgetRequest2015.docx. Follow the instructions on the form to submit. Even if you click 'Yes' to this question, the form will no longer proceed to the Clinical Research Services (CRS) Application Form section.

8 Yes m No

26.2 This project involves community-based research:

m Yes 8 No

26.3 This project involves practice-based research:

m Yes 8 No

27.0 End of Study Application

27.1 End of Study Application Form To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.