PROTOCOL TITLE:

Home-based physical therapy intervention to decrease frailty in liver transplant candidates

PRINCIPAL INVESTIGATOR:

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NCT04836923

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	N/A
IND / IDE / HDE #	N/A
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☒ Adults Unable to Consent ☒ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	500
Funding Source	None
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC) *All data will be collected at NMH
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVES:

Frailty is a significant problem in patients undergoing liver transplant and is associated with poor outcomes and survival. Hence, optimizing physical fitness and counteracting frailty is important. However, many interventions are very resource intensive and therefore not feasible.

In this study, we aim to test the effectiveness of a newly designed intervention to improve frailty in liver transplant candidates. The "LIver FrailTy" intervention (LIFT) will consist of an evaluation by a physical therapist, an individualized home exercise prescription (HEP), exercise tracking using a smart phone application, daily text reminders to exercise and recurrent telephone check-ins. We also aim to perform "Realistic Effort Action Planning" (REAP), which is a form of personality-informed motivational interviewing, in a subset of patients to determine if this enhances the LIFT intervention.

Aim 1: To evaluate the feasibility of the LIFT and REAP interventions in patients evaluated for liver transplantation.

Aim 2: To measure the effect of the LIFT and REAP intervention on frailty in patients evaluated for liver transplantation.

Aim 3: To evaluate barriers to the implementation of the LIFT and REAP interventions

Aim 4: To analyze the effects of LIFT and REAP on pre- and post-liver transplant clinical outcomes.

BACKGROUND:

Frailty is defined as a biologic syndrome of decreased physiologic reserve and increased vulnerability to health stressors. The concept of frailty has recently emerged as a critical determinant in the field of cirrhosis and liver transplantation. Frailty impacts pre- and post-transplant clinical outcomes, including waitlist mortality, post-transplant mortality, frequency of hospitalizations and duration of hospital admissions. Although the impact of frailty in liver transplantation has been established in the literature, there is a lack of data supporting effective interventions to decrease frailty prior to liver transplantation. Moreover, the studies that have tested interventions to improve physical function have relied on frequent supervised physical therapy sessions and access to exercise equipment that it is not financially or logistically feasible for the majority of patients. Patient engagement in PT also remains a critical barrier to overcome to decrease frailty in preparation for liver transplantation. Developing a practical and effective intervention to consistently engage patients in physical activity and decrease frailty is essential to improving clinical outcomes in the pre- and post-liver transplant setting.

Our goal is to pilot test a novel PT intervention to decrease frailty in pre-transplant patients. We have designed a prototype "LIver FrailTy" intervention (LIFT) that includes: PT evaluation, an individualized home exercise prescription (HEP), daily text message reminders to exercise and weekly telephone check-ins with team members. We will also employ "Realistic Effort Action Planning" (REAP), a form of personality-informed motivational interviewing in a subset of patients to potentially enhance patient engagement and adherence to the home-exercise prescription.

Our central hypothesis is that our LIFT (+/- REAP) intervention will 1) improve adherence to recommended levels of exercise in end-stage liver disease 2) reduce pre-transplant frailty and 3) will improve pre- and post-transplant clinical outcomes.

STUDY ENDPOINTS:

Primary endpoints:

- Frailty (measured by Liver frailty index [LFI])
- Clinical outcomes: placement on LT waitlist, waitlist-mortality, post-transplant mortality, post-transplant disposition (acute rehabilitation, subacute rehabilitation center, home, etc), number of hospitalizations, duration of hospitalizations, liver related complications (ascites, hepatic encephalopathy, variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome, infections).
- Feasibility (measured by 8-question emailed survey)

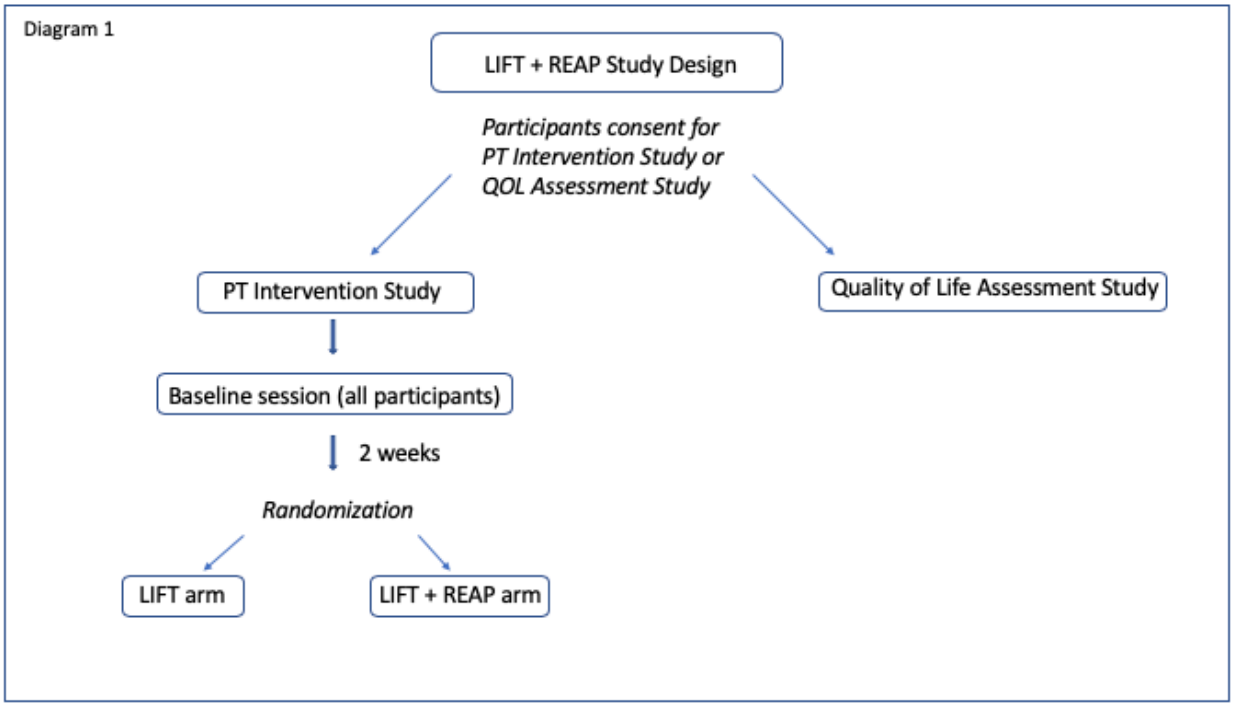
Secondary endpoints:

- Endurance (measured by the 4-meter walk test).
- Patient adherence to the home exercise prescription (measured by daily diary counts of adherence to prescribed exercises, tracked on the TrueCoach application)
- Degree of hepatic encephalopathy (measured by List Sort Working Memory [LSWM] test and the Flanker Inhibitory Control and Attention [FICA])
- Patient-reported quality of life (measured by various PROMIS questionnaires)
- Feasibility/acceptability (measured by a study-specific questionnaire evaluating the acceptability and feasibility as reported by patients, providers and support staff)

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):

Home exercise prescription (HEP) detailed below in study design.

PROCEDURES INVOLVED:



Recruitment for Quality of Life Assessment Study:

- A Northwestern Medicine Enterprise Data Warehouse (NMEDW) search will be used to identify all patients who have been seen in Transplant Evaluation Clinic and are currently being considered for liver transplantation or are already on the waitlist or have received a transplant.
- Alternatively, a list of the patients described above will be obtained from the transplant coordinator.
- Patients will be called directly to introduce the study (script attached). A treatment relationship already exists with these patients, making an opt out letter unnecessary. If patients are interested in participating, consent will be obtained verbally. This verbal consent form is attached to the study submission. The consent form will be reviewed over the phone. Patients or their POA will provide their consent verbally, and the study team will document in the study records. A copy of this consent form will be mailed to each patient.
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Recruitment for PT Intervention Study

- The Hepatology Clinic (Tuesday AM) schedule and the Transplant Evaluation Clinic (Thursday AM) schedule will be used to identify patients who are scheduled to be seen in clinic within 1 month. On a weekly basis, patients will be called directly to introduce the study (script attached). A treatment relationship already exists with these patients, making a recruitment letter unnecessary. If patients are interested in participating, consent will be obtained electronically. This consent form will be the same as the written consent form (attached). The link to this document will be emailed or texted to patients. The consent form will be reviewed over the phone. Patients or their POA will provide their e-signature and the date of consent, which will be acquired via REDCap. A copy of this consent form will be e-mailed to each patient.
- If unable to contact patients prior to their scheduled appointment, recruitment will also take place in Hepatology Clinic and Transplant Evaluation Clinic. In this case, informed consent will be obtained will be obtained from patients or their present POA on an Ipad (via REDCap) before any research activities (attached).
- Patients will also be recruited if admitted to Northwestern Memorial Hospital and identified as transplant candidates or undergoing an expedited transplant evaluation. Consent will be obtained in person using an Ipad as documented above.

All participants who enroll in the PT intervention study -

Baseline session:

- Baseline clinical data will be collected at time of enrollment via the NMEDW and via chart review (will submit EDW exception). Data will include: Age, gender, race, ethnicity, body mass index (BMI), employment status, education, marital status, etiology of liver disease, complications of liver disease (ascites, hepatic encephalopathy, presence of esophageal/gastric varices, history of variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome), medical history (coronary artery disease, chronic kidney disease, dialysis dependence, hypertension, hyperlipidemia), and baseline laboratory data (platelets, serum sodium, serum creatinine, PT/INR, total bilirubin, albumin, calculated MELD) (Appendix A, B)
- Components of baseline session: (1) personality assessment (2) patient-reported quality of life assessment (3) hepatic encephalopathy assessment (4) frailty assessment, (5) physical therapy introduction.

- Personality assessment
  - Setting:
    - If consented over the phone prior to clinic visit, the personality survey will be emailed/texted to patients and completed over the telephone with a team member.
    - If consented in clinic visit or while admitted inpatient, the personality survey will be completed in clinic or at bedside with a team member.
  - Tool: Modified Midlife Development Inventory (MIDI) Personality Scale
  - Time: 38 questions, 3-5 minutes
  - Data collected via REDcap
  - Appendix C

- Patient-reported quality of life assessment (in clinic)
  - Setting:
    - If consented over the phone prior to clinic visit, the QOL survey will be emailed/texted to patients and completed over the telephone with a team member.
    - If consented in clinic visit or while admitted inpatient, the QOL survey will be completed in clinic or at bedside with a team member.
  - Tools: PROMIS surveys: Physical function – Short form 8c, Cognitive Function
  - Time: ~15 questions, 5 minutes
  - Data collected via REDcap
  - Appendix D

- Hepatic encephalopathy assessment
  - Setting: in clinic or at bedside if inpatient.
  - Tools: List Sort Working Memory (LSWM) test, the Flanker Inhibitory Control and Attention (FICA) test, Pattern Comparison Processing Speed Test administered on ipad and keyboard.
  - Time: 16 minutes (LSWM – 7 minutes, FICA – 3 minutes, PCPS – 3 minutes)
  - Appendix E

- Frailty assessment
  - Setting: in clinic or at bedside if inpatient.
  - Tools: Liver Frailty Index, 4-meter walk test
    - Balance testing
    - Repeat chair stands
    - Grip testing
  - This is performed in all patients in clinic, regardless of whether they consent for this study specifically.
  - Time: 5 minutes
  - Appendix F

- Physical therapy introduction
  - Setting: in clinic or at bedside if inpatient.
  - Provide equipment (weights, therabands, dynamometer, Truecoach smart phone application if not installed over the phone after consent was received)

- Demonstrate initial home exercise prescription, which will include a set of exercises to be done at home on a daily basis (cardio exercises, resistance exercises). These recommended exercises will be within standard of care.
- Time: 10-15 minutes

LIFT subgroup:

Follow up:

- *Text reminders (every day):*
  - An automated system will be used to generate and send daily text messages reminding patients to follow their HEP. Texts will be standardized and not contain any PHI.

- *Exercise data collection (continuously):*
  - Data continuously collected via TrueCoach smart phone application to document adherence to exercise regimen. If patients are unable to appropriately track adherence on the smart phone application, this data will be collected at weekly videoconference/telephone check-ins detailed below.

- *LFI calculation at home (every 4 weeks)*
  - A dynamometer will be given to each patient at time of enrollment. A video will be uploaded on the TrueCoach application demonstrating how to perform grip strength testing.
  - Balance testing and chair stands will be tested at home.
  - A team member will walk patients through each test via a videoconference call.

- *Patient-reported quality of life assessment at home (every 4 weeks, surveys emailed - Patients will be called by a team member who will walk the patient through the survey and record data over the phone)*
  - Tools: PROMIS surveys: Physical function – Short form 8c, Cognitive Function
  - Data collected via REDcap

- *Personality assessment at home (every 4 weeks, survey emailed - Patients will be called by a team member who will walk the patient through the survey and record data over the phone)*
  - Tool: Modified Midlife Development Inventory (MIDI) Personality Scale
  - Data collected via REDcap

- *Videoconference/telephone check-in (every 1 week):*
  - Performed by a member of the research team.
    - If patients are unable to track adherence to exercise regimen via TrueCoach application, the team member will document daily physical activity on this call.
    - If patients have questions regarding exercise regimen, they will be contacted by a physical therapist.
  - Progress reviewed and exercise regimen potentially adjusted by a physical therapist based on data collected and patient experience.

- *Clinical data collection via NEDW and review of EMR (every 4 weeks)*
  - Number of hospitalizations, intensive care unit admissions, duration of hospitalizations, development of decompensating events (ascites, hepatic

encephalopathy, variceal bleeding), transplant status, type of LT (living donor LT, simultaneous liver-kidney), duration of hospital admission for LT, duration of ICU admission for LT, duration of intubation post-LT, post-transplant discharge disposition, date of death, cause of death, post-transplant complications (rejection, infection, biliary complications).

- *Clinic visits (every 3 months, same tools as noted above)*
    - Patient-reported quality of life assessment
    - Hepatic encephalopathy assessment
    - Frailty assessment, 4-meter walk test (standard of care)
    - Physical therapy in person update (standard of care)
    - Data collection via NMEDW extraction and chart review: Number of hospitalizations, intensive care unit admissions, duration of hospitalizations, development of decompensating events (ascites, hepatic encephalopathy, variceal bleeding), transplant status, type of LT (living donor LT, simultaneous liver-kidney), duration of hospital admission for LT, duration of ICU admission for LT, duration of intubation post-LT, post-transplant discharge disposition, date of death, cause of death, post-transplant complications (rejection, infection, biliary complications).

- Feasibility assessment (for those who remain in the study for atleast 1 month or until receiving a liver transplant; surveys emailed)
    - Tool: 8 -question survey emailed to eligible subjects as noted above.
    - Data collected via REDCap.
    - Time: < 3 minutes
    - Appendix G

All participants who enroll for the PT intervention will be randomized (1:1) into the LIFT subgroup or the LIFT + REAP subgroup at 2 weeks after enrollment/baseline session. The LIFT subgroup will continue to follow up as detailed above. The LIFT + REAP subgroup will undergo Realistic Effort Action Planning (REAP), which is described below:

LIFT + REAP subgroup:

Follow up:

- *REAP introduction (2 weeks after enrollment, via telephone/videoconference, time: 30 minutes)*
    - Performed by a member of the research team.
    - Patients will be asked to reflect on their experience with the HEP.
    - Discussion of barriers to engaging in HEP and how to overcome them.
    - Reflection on past experiences with obstacles outside of exercise that required patients to exert a lot of effort and how they were able to accomplish it.
    - How can you apply these strategies to your exercise goals?
    - Introduce action plans.
    - Discussion of industriousness and how to apply learned industriousness to exercise-related goal achievement.
    - Discuss building increments to get to exercise goals.
    - Identify the threshold for sustained effort where patients can still reach their goal.

  - Instruct patients to document level of effort for each day of exercise and refer to them as needed. Patients will document effort in TrueCoach application via comments section.
    - 1 = no exertion at all
    - 2 = very light
    - 3 = somewhat hard (but still feels OK to continue)
    - 4 = very hard (strenuous)
    - 5 = maximal exertion

- *Text reminders (every day):*
  - An automated system will be used to generate and send daily text messages reminding patients to follow their HEP. Texts will be standardized and not contain any PHI.

- *Exercise data collection (continuously)*
  - Data continuously collected via TrueCoach application to document adherence to exercise regimen. If patients are unable to appropriately track adherence on application, this data will be collected at weekly videoconference/telephone check-ins detailed below.

- *LFI calculation at home (every 4 weeks)*
  - A dynamometer will be given to each patient at time of enrollment. A video will be uploaded on the TrueCoach application demonstrating how to perform grip strength testing.
  - Balance testing and chair stands will be tested at home.
  - A team member will walk patients through each test via a videoconference call.

- *Patient-reported quality of life assessment at home (every 4 weeks, surveys emailed - Patients will be called by a team member who will walk the patient through the survey and record data over the phone)*
  - Tools: PROMIS surveys: Physical function – Short form 8c, Cognitive Function
  - Data collected via REDcap

- *Personality assessment at home (every 4 weeks, survey emailed - Patients will be called by a team member who will walk the patient through the survey and record data over the phone)*
  - Tool: Modified Midlife Development Inventory (MIDI) Personality Scale
  - Data collected via REDcap

- *Videoconference/telephone check-in (every 1 week)*
  - Performed by a member of the research team.
    - If patients are unable to track adherence to exercise regimen via TrueCoach application, the team member will document daily physical activity on this call.
    - If patients have questions regarding exercise regimen, they will be contacted by a physical therapist.
  - Progress reviewed and exercise regimen potentially adjusted by physical therapist based on data collected and patient experience.
  - REAP follow up (time: 5-15 minutes):
    - Reflect with patient on previous action plan and level of realistic sustained effort put forward in the past week.

        - Encourage patient to adjust action plan according to perceived threshold of sustained effort.

- *Clinical data collection via NEDW and review of EMR (every 4 weeks)*
    - Number of hospitalizations, intensive care unit admissions, duration of hospitalizations, development of decompensating events (ascites, hepatic encephalopathy, variceal bleeding), transplant status, type of LT (living donor LT, simultaneous liver-kidney), duration of hospital admission for LT, duration of ICU admission for LT, duration of intubation post-LT, post-transplant discharge disposition, date of death, cause of death, post-transplant complications (rejection, infection, biliary complications).

- *Clinic visits (every 3 months, same tools as noted above)*
    - Patient-reported quality of life assessment
    - Hepatic encephalopathy assessment
    - Frailty assessment, 4-meter walk test
    - Physical therapy in person update

- Feasibility assessment (for those who remain in the study for atleast 1 month or until receiving a liver transplant; surveys emailed)
    - Tool: 8-question survey emailed to eligible subjects as noted above.
    - Data collected via REDCap.
    - Time: < 3 minutes
    - Appendix G

Audio/Video Recording:
All telephone calls and videoconference calls between team members and patients will be recorded. Recording will be necessary to ensure standardization of follow up communications. This is critical in the pilot study to eliminate confounding factors between the LIFT and LIFT+REAP subgroups. Only IRB approved personnel will have access to the data. All data will be stored on FSM shared drive-accessed only by approved personnel. All data is accessed through password protected computer kept in locked offices. All patent identifiers will be stored in a separate password protected file. All recordings will be deleted within 3 years of study completion.

Retrospective Control group for those who enroll in the PT intervention study:

- A list of all patients who were evaluated for liver transplantation at Northwestern Memorial Hospital from January 1st 2018 through October 26th, 2020 will be drawn from the EDW.
- Baseline Clinical data will be collected via the EDW and via chart review. Data will include: Age, gender, race, ethnicity, body mass index (BMI), employment status, education, marital status, etiology of liver disease, complications of liver disease (ascites, hepatic encephalopathy, presence of esophageal/gastric varices, history of variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome), medical history (coronary artery disease, chronic kidney disease, dialysis dependence, hypertension, hyperlipidemia), and baseline laboratory data (platelets, serum sodium, serum creatinine, PT/INR, total bilirubin, albumin, calculated MELD). No data will be collected that is not already existing in the EMR at the date of IRB submission.
- Follow up data will be extracted retrospectively from the EDW and via chart review. Follow up data will include: Number of hospitalizations, intensive care unit admissions, duration of hospitalizations, duration of intensive care unit admission, development of decompensating

events (ascites, hepatic encephalopathy, presence of esophageal/gastric varices, history of variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome, infections), transplant status, date of death, cause of death, placement on LT waitlist, delisting from LT waitlist, date of transplant, type of LT (living donor LT, simultaneous liver-kidney), duration of hospital admission for LT, duration of ICU admission for LT, duration of intubation post-LT, post-transplant discharge disposition, post-transplant complications (rejection, infection, biliary complications, hypertension, hyperlipidemia,), liver frailty index scores, Karnofsky Performance Status Scores, body mass index (BMI), and laboratory data (platelets, serum sodium, serum creatinine, PT/INR, total bilirubin, albumin, calculated MELD). No data will be collected that is not already existing in the EMR at the date of IRB submission.

- A waiver of consent will be requested for this retrospective EDW data extraction. It meets criteria for a waiver of consent as listed on the IRB website: 1) The research is not FDA regulated. 2) The research does not involve non-viable neonates. 3) The research involves no more than minimal risk to subjects. 4) The waiver or alteration will not adversely affect the rights and welfare of the subjects. 5)The research could not be practicably carried out without the waiver. Patients will not be required to complete any tasks as part of the control study and will not be subject to any risks. Seeing as there are approximately 300 patients who have received a liver transplant at Northwestern since 1/2018, it would be impractical to consent each patient. Moreover, many patients have passed away or likely no longer follow up closely at Northwestern. Obtaining consent from these deceased patients would be impossible and obtaining consent from patients who no longer follow at NMH would be very difficult. Although consent could be obtained from deceased patients' families, this could adversely affect the rights of privacy for these families and cause more emotional harm. 6) The research could not be carried out without using private information in an identifiable format. 7) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Participants who enroll in the Quality of Life Assessment Study:

Baseline session:

- Baseline clinical data will be collected at time of enrollment via the NMEDW and via chart review. Data will include: Age, gender, race, ethnicity, body mass index (BMI), employment status, education, marital status, etiology of liver disease, complications of liver disease (ascites, hepatic encephalopathy, presence of esophageal/gastric varices, history of variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome), liver frailty index scores, Karnofsky Performance Status Scores, MELD scores, medical history (coronary artery disease, chronic kidney disease, dialysis dependence, hypertension, hyperlipidemia), and baseline laboratory data (platelets, serum sodium, serum creatinine, PT/INR, total bilirubin, albumin, calculated MELD) (Appendix A, B)

- Personality assessment
    - Setting: Surveys will be administered via Redcap. Survey links will be emailed to patients. Reminder emails will be sent if no response is received. Surveys may be completed over the telephone with a team member if no response is received to email, or if the patient requires assistance.
    - Tool: Modified Midlife Development Inventory (MIDI) Personality Scale
    - Time: 38 questions, 3-5 minutes
    - Appendix C

- Patient-reported quality of life assessment
    - Setting: See setting of personality assessment above.
    - Tools: PROMIS surveys: Global 10, Physical Function, Cognitive Function, Fatigue, Pain, Dyspnea, Spiritual Health and Social Activities.
    - Time: ~34 questions, 10 minutes
    - Appendix D

Follow up:

- Personality assessment
    - Setting: Surveys will be administered via Redcap. Survey links will be emailed to patients. Reminder emails will be sent if no response is received. Surveys may be completed over the telephone with a team member if no response is received to email, or if the patient requires assistance.
    - Tool: Modified Midlife Development Inventory (MIDI) Personality Scale
    - Time: 38 questions, 3-5 minutes
    - Appendix C

- *Patient-reported quality of life assessment at home (every 4 weeks)*
    - Setting: See setting of personality assessment above.
    - Tools: PROMIS surveys: Global 10, Physical Function, Cognitive Function, Fatigue, Pain, Dyspnea, Spiritual Health and Social Activities.
    - Time: ~34 questions, 10 minutes
    - Appendix D

- *Data collection via NEDW and review of EMR (every 4 weeks)*
    - Number of hospitalizations, intensive care unit admissions, duration of hospitalizations, duration of intensive care unit admission, development of decompensating events (ascites, hepatic encephalopathy, presence of esophageal/gastric varices, history of variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome, infections), transplant status, date of death, cause of death, placement on LT waitlist, delisting from LT waitlist, date of transplant, type of LT (living donor LT, simultaneous liver-kidney), duration of hospital admission for LT, duration of ICU admission for LT, duration of intubation post-LT, post-transplant discharge disposition, post-transplant complications (rejection, infection, biliary complications, hypertension, hyperlipidemia), liver frailty index scores, Karnofsky Performance Status Scores, body mass index (BMI), and laboratory data (platelets, serum sodium, serum creatinine, PT/INR, total bilirubin, albumin, calculated MELD).

DATA AND SPECIMEN BANKING

Data/specimens will not be banked for future use.

The data collected in this study will also be used in the Functional Assessment in Liver Transplantation study (STU00203582), The Role of Circadian Dysfunction in Hepatic Encephalopathy in Patients with Cirrhosis study (STU00204423), and the Personality, QOL and Frailty in Liver Transplantation study (STU00212668).

SHARING RESULTS WITH PARTICIPANTS

Study results will not be shared with participants or anyone else.

STUDY TIMELINES

Patients will be prospectively enrolled in the study from 9/13/2020 vs date of IRB approval to 7/31/2025. Patients in the Quality of Life Assessment arm will remain enrolled in the study while on the liver transplant waitlist and until 3 years after liver transplantation or up to a maximum of 5 years if not listed for liver transplantation. Patients in the PT Intervention arm will remain enrolled in the study while on the liver transplant waitlist and until 1 year after liver transplantation or up to a maximum of 5 years if not listed for liver transplantation. The estimated date for completion of primary analyses is 9/1/2025.

INCLUSION AND EXCLUSION CRITERIA

PT Intervention Study

Inclusion (criteria will be confirmed during consent process and during in-clinic physical therapy evaluation)

- Patients with a diagnosis of liver cirrhosis being evaluated for liver transplantation in hepatology/transplant evaluation clinic
- English-speaking
- Patients with access to a smart phone, tablet or computer (with videoconference capabilities)
- Vulnerable populations: We will include patients who are cognitively impaired due to hepatic encephalopathy and unable to consent for themselves.

Exclusion:

- Patients < 18 years of age
- Patients without the ability to consent for themselves or through a medical power of attorney.

Quality of Life Assessment Study

Inclusion (criteria will be confirmed during consent process)

- Patients with a diagnosis of liver cirrhosis who have been seen in Transplant Evaluation Clinic, and are currently being considered for liver transplantation or are already on the waitlist or have received a transplant
- English-speaking
- Vulnerable populations: We will include patients who are cognitively impaired due to hepatic encephalopathy and unable to consent for themselves.

Exclusion

- Patients < 18 years of age
- Patients without the ability to consent for themselves or through a medical power of attorney.

If patients are unable to consent for themselves, consent will be obtained from his or her designated POA (as detailed below). We are including these patients in our study because hepatic encephalopathy a complication of cirrhosis and is one of our secondary endpoints.

VULNERABLE POPULATIONS

For patients that are cognitively impaired from hepatic encephalopathy, a neurological complication of liver disease, the Principal Investigator and Co-Investigators, who have clinical training in how to judge capacity in vulnerable populations, will make the determination of whether a patient with a history of this cognitive impairment can consent. The consent process for these individuals will inform the subject about the research to the extent compatible with the subject's understanding. These subjects will be assessed at regular intervals (at each follow-up assessment) during their participation to ensure their capacity for consent. If they lose their capacity to consent, as determined by the PI and/or Co-Investigators, they will need to be re-consented with a POA/LAR consent on their behalf. If they were enrolled with a POA/LAR, and gain the capacity to consent as determined by the PI and/or Co-Investigators, then they will be re-consented.

If a patient appears unduly distressed, they will be withdrawn from the study.

PARTICIPANT POPULATION(S)

The only vulnerable population included in this study are cognitively impaired patients who do not have capacity to consent for themselves.

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Total:	All groups (unclear how many patients will be unable to consent for themselves)	500	500

RECRUITMENT METHODS

Recruitment for Quality of Life Assessment Study:

- A Northwestern Medicine Enterprise Data Warehouse (NMEDW) search will be used to identify all patients who have been seen in Transplant Evaluation Clinic and are currently being considered for liver transplantation or are already on the waitlist or have received a transplant.
- Alternatively, a list of the patients described above will be obtained from the transplant coordinator.
- Patients will be called directly to introduce the study (script attached). A treatment relationship already exists with these patients, making a recruitment letter unnecessary. If patients are interested in participating, consent will be obtained verbally. This verbal consent form is attached to the study submission. The consent form will be reviewed over the phone. Patients or their POA will provide their consent verbally, and the study team will document in the study records. A copy of this consent form will be mailed to each patient.

Recruitment for PT Intervention Study

- The Hepatology Clinic (Tuesday AM) schedule and the Transplant Evaluation Clinic (Thursday AM) schedule will be used to identify patients who are scheduled to be seen in clinic within 1 month. On a weekly basis, patients will be called directly to introduce the study (script attached).

A treatment relationship already exists with these patients, making a recruitment letter unnecessary. If patients are interested in participating, consent will be obtained electronically. This consent form will be the same as the written consent form (attached). The link to this document will be emailed or texted to patients. The consent form will be reviewed over the phone. Patients or their POA will provide their e-signature and the date of consent, which will be acquired via REDCap. A copy of this consent form will be e-mailed to each patient.

- If unable to contact patients prior to their scheduled appointment, recruitment will also take place in Hepatology Clinic and Transplant Evaluation Clinic. In this case, informed consent will be obtained on an Ipad (via RedCAP) from patients or their present POA before any research activities (attached).
- Patients will also be recruited if admitted to Northwestern Memorial Hospital and identified as transplant candidates or undergoing an expedited transplant evaluation. Consent will be obtained in person using an Ipad as documented above.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participants will not be compensated for their participation in this study.

WITHDRAWAL OF PARTICIPANTS

Patients will not be withdrawn from the study unless they request withdrawal themselves or if it is determined that it is in the best interest of patients' health and welfare to stop. Patients who are cognitively impaired will be withdrawn from the study if they appear unduly distressed.

RISKS TO PARTICIPANTS

PT Intervention Study:

Falls or muscle strains while exercising at home and during the measurement of liver frailty index are a risk involved in the study.

- This risk will be minimized by the presence of trained physical therapists during LFI testing in clinic.
- Detailed instructions on exercise plans will be provided to minimize the risk of falls at home. Potential concerns regarding exercises will be addressed during weekly calls with the research team. Physical therapists will be available to speak with patients about exercises throughout the study course.
- The exercises recommended for study participants will be similar to the exercises recommended to all patients being evaluated for liver transplantation, regardless of study participation. This is part of the standard of care and is thus, not a significant risk of the study itself.

PT *Intervention Study and QOL Assessment Study:*

A confidentiality breach is a risk associated with data review research. All necessary precautions will be done to prevent a confidentiality breach as per FSM data security policy.

- All electronic versions of data sets will be kept in password protected computers on a password protected server with access only to the project investigators and project staff. Subjects' names will be kept in a separate file from any findings by using a unique study code number for each participant.

- Only the principal investigator and co-investigators listed on this study will have access to harvested patient data.
- Any documents containing identifiable information will be destroyed within five years of project completion using electronic "shredding" software.

POTENTIAL BENEFITS TO PARTICIPANTS

PT Intervention Study:

Improvement in physical function (decreased frailty), which should improve pre- and post-transplantation outcomes, is the primary benefit of participating in the study. Based on the current literature demonstrating the negative impact of frailty on clinical outcomes in liver transplantation, improvement in clinical outcomes with improvement in physical function is likely.

QOL Assessment Study:

There is no direct benefit to participation.

DATA MANAGEMENT AND CONFIDENTIALITY

Only IRB approved personnel will have access to the data. All data will be stored on FSM shared drive-accessed only by approved personnel. All data is accessed through password protected computer kept in locked offices. All patent identifiers will be stored in a separate password protected file.

These data will be presented at national meetings (i.e. American Transplant Congress, etc) and a manuscript will be written for consideration of publication in respected, peer-reviewed journals (i.e. American Journal of Transplantation). All publications will include only aggregated data and no patient identifiers will ever be reported. Data will be stored until 3 years after the end of the project and will be destroyed.

QOL Assessment study
As PHI will be collected under a waiver of written HIPAA authorization, the PHI collected for these participants will not be reused or disclosed to any other person or entity, and the identifiers will be destroyed at the time of IRB closure.

Statistical analysis:

Chi-squared tests will be used to assess differences in categorical clinical endpoints and T-tests will be used to assess differences in continuous clinical endpoints between the LIFT and LIFT + REAP subgroups. Multivariate analysis will be used to assess clinical factors associated with clinical endpoints in each group. Survival analysis will be conducted after controlling for all the variables that are significant during regression analysis.

In order to detect statistical differences between the two study arms, as well as correlation between personality traits, quality of life, frailty, hepatic encephalopathy and patient characteristics (age, primary diagnosis, MELD, etc), we expect that a sample size of 500 should be suitable for this pilot study.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Safety of the intervention, specifically risk of falls and muscle strains, will be assessed on a weekly basis with telephone calls to each participant. Physical therapist will tailor exercise regimens to each patient's physical function in order to minimize risk of falls. The safety of the intervention will be assessed at bi-monthly research team meetings.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Only research team members will contact participants once they enroll in the study. The frequency of communication will be clearly outlined to each participant prior to enrollment to ensure appropriate expectations.

Only IRB approved personnel will have access to the data. All data will be stored on FSM shared drive-accessed only by approved personnel. All data is accessed through password protected computer kept in locked offices. All patent identifiers will be stored in a separate password protected file.

All publications will include only aggregated data and no patient identifiers will ever be reported. Data will stored until 3 years after the end of the project and will be destroyed.

COMPENSATION FOR RESEARCH-RELATED INJURY
None

ECONOMIC BURDEN TO PARTICIPANTS
None

CONSENT PROCESS

PT Intervention participants
Informed consent will be obtained from patients or their POA prior to any data collection. Consent will be obtained by research coordinators or other members of the research team using an online consent form or in Hepatology and Transplantation Evaluation Clinic, where patients will be enrolled. Dedicated time will be reserved for after the visit to explain the research study and highlight risks/benefits. Participants will be asked to summarize their own understanding of the study, as well as potential risks/benefits, in order to ensure capacity to enroll. Consent will be obtained in English if the patient is English-speaking.

A waiver of consent will be requested for the retrospective EDW data extraction for the historical control group. It meets criteria for a waiver of consent as listed on the IRB website: 1) The research is not FDA regulated. 2) The research does not involve non-viable neonates. 3) The research involves no more than minimal risk to subjects. 4) The waiver or alteration will not adversely affect the rights and welfare of the subjects. 5)The research could not be practicably carried out without the waiver. Patients will not be required to complete any tasks as part of the control study and will not be subject to any risks. Seeing as there are approximately 300 patients who have received a liver transplant at Northwestern since 1/2018, it would be impractical to consent each patient. Moreover, many patients have passed away or likely no longer follow up closely at Northwestern. Obtaining consent from these deceased patients would be impossible and obtaining consent from patients who no longer follow at NMH would be very difficult. Although consent could be obtained from deceased patients' families, this could adversely affect the rights of privacy for these families and cause more emotional harm. 6) The research could not be carried out without using private information in an identifiable format. 7) Whenever

appropriate, the subjects will be provided with additional pertinent information after participation.

QOL Assessment participants
Informed consent will be obtained from patients or their POA prior to any data collection. Consent will be obtained by research coordinators or other members of the research team using a verbal consent process over the phone, where patients will be enrolled. Dedicated time will be reserved to explain the research study and highlight risks/benefits. Participants will be asked to summarize their own understanding of the study, as well as potential risks/benefits, in order to ensure capacity to enroll. Consent will be obtained in English if the patient is English-speaking.

NON-ENGLISH SPEAKING PARTICIPANTS

Non-English speakers will not be included in this study.

WAIVER OR ALTERATION OF CONSENT PROCESS

- ***Adults Unable to Consent or Cognitively Impaired Adults:***

  - Consent will be required for all participants.
  - Ability to provide consent will be assessed by the research team member introducing the research study and obtaining consent. Patients' capacity to consent will be assessed by asking the patients to clearly state the purpose of the study and what the study entails. They will be asked to outline the potential benefits and consequences of the study. They will be assessed on their understanding that the study is voluntary and their understanding that deciding not to participate will not impact their medical care negatively in any way.
  - If a participant is unable to provide consent, consent will be obtained from the participant's durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child, in this order.
  - If a patient is determined to not have capacity to provide consent, the research study will still be explained to the patient in a level suitable to their understanding.

- ***Process to Document Consent in Writing***

  PT Intervention participants
  Please see Written Consent Form attached. This is the separate consent form for the LIFT+/-REAP study.

  QOL Assessment participants
  Please see the Verbal Consent form. This is the separate consent form for the QOL assessment study.

  The researchers request a waiver of written consent for the QOL assessment study participants. The verbal consent form contains all elements of consent disclosure, and the QOL assessments are minimal risk. Interventions are limited to surveys and an EDW query of their medical records. These interventions would not require consent in a standard clinical context.

Moreover, the researchers have found that eConsent has not been practicable for the study population, which is generally elderly, chronically ill, and not technically savvy. As such, the researchers estimate that 30% of study candidates have been lost due to technical difficulties with the eConsent process.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

- This study does involve the creation and use of PHI.
- HIPAA authorization will be obtained from all patients seen in Hepatology and Transplantation Evaluation Clinic, the setting in which participants are recruited.
- Specific PHI to be obtained from the EDW and chart review are outlined in Appendix A, B.

- QOL Assessment participants
  The researchers request a waiver of written HIPAA authorization for the QOL assessment study participants. The researchers have found that electronic HIPAA authorization has not been practicable for the study which is generally elderly, chronically ill, and not technically savvy. As such, the researchers estimate that 30% of study candidates have been lost due to technical difficulties with the electronic HIPAA authorization process.

  This study could not be practicably conducted without access to the participants' PHI. The variables (described on page 10) are required to assess correlation between survey responses and clinical outcomes. The clinical variables are also required to control for confounders when analyzing survey data. Therefore, access to PHI is critical to the goals of this study.

  Finally, the use of the PHI is of no more than minimal risk to the participants. The NM EDW will be used to query the participants' medical records and data will be kept on an FSM managed server. For more information, please refer to the "DATA MANAGEMENT AND CONFIDENTIALITY" section of this protocol. The PHI collected for these participants will not be reused or disclosed to any other person or entity, and the identifiers will be destroyed at the time of IRB closure.
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QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

- Given the number of patients seen in Hepatology (10 patients)/Transplantation Evaluation Clinic (8 patients) on a weekly basis, it will be feasible to recruit the required number of patients necessary for the study.
- The study will be conducted and completed by a research team under the leadership of the Principle Investigator, Dr. Daniela Ladner. Study analysis will be performed by Dr. Avesh Thuluvath (dedicated T32 research fellow) and Osama Siddiqui (dedicated research medical student).
- Outside of surveys and testing completed in clinic, no other facilities/resources will be required for this study.
- All members of the research team will review the study protocol to ensure that they are informed of research procedures as well as their individual duties and functions.

MULTI-SITE RESEARCH

This is not a multi-center study.