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Technology Enabled Strategies to promote Treatment adherence in Liver Transplantation: Rationale and Design of the TEST Trial

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Abstract

Background and Aims: Liver transplantation is a life-saving procedure for end-stage liver disease. However, post-transplant medication regimens are complex and non-adherence is common. Post-transplant medication non-adherence is associated with graft rejection, which can have long-term adverse consequences. Transplant centers are equipped with clinical staff that monitor patients post-transplant; however, digital health tools and proactive immunosuppression adherence monitoring has potential to improve outcomes.

Methods and Analysis: This is a patient-randomized prospective clinical trial at 3 transplant centers in the Northeast, Midwest, and South to investigate the effects of a remotely-administered adherence program compared to usual care. The program monitors potential non-adherence largely levering text message prompts and phenotypes the nature of the non-adhere as cognitive, psychological, medical, social, or economic. Additional reminders for medications, clinical appointments and routine self-management support are incorporated to promote adherence to the entire medical regimen. The primary study outcome is medication adherence; secondary outcomes include quality of life, functional health status, and clinical outcomes (e.g. days hospitalized). Study implementation, acceptability, feasibility, costs and potential cost-effectiveness will also be evaluated.

Ethics and Dissemination: The University of Pennsylvania Review Board has approved the study as the single IRB of record (protocol # 849575, V1.4). Results will be published in peer-reviewed journals and summaries will be provided to study funders.

Registration: NCT05260268

Article Summary:

Strengths and limitations of this study

- This is a multi-center trial conducted in English and Spanish that includes de-novo liver and liver/kidney transplant recipients.
- We will assess efficacy as well as implementation outcomes and costs.
- Limitations include that clinical trial participants may be more engaged than average.
- Findings may not apply to settings that do not use electronic health records or to patients who do not own or use cellphones.

Introduction

Liver transplant (LT), while providing a substantial survival benefit for decompensated liver disease, is a costly and limited resource[1–4]. With advances in surgical techniques and immunosuppression (IS), 5-year post-transplant survival exceeds 70%[5]. However, liver transplant recipients (LTRs) manage complex immunosuppression regimens to maintain graft function. LTRs must navigate complex health-systems, adhere to lifestyle changes, clinical monitoring, and take multiple medications with potential side effects and frequent dosing changes[6,7], all requiring robust health literacy and self-management skills. LTRs take on average 11 medications and 39% report a medication change within the past 30 days[6]. Additionally, 38% of LT candidates have inadequate health literacy[8], and lower health literacy is associated with poor treatment knowledge and higher IS nonadherence[6,9].

Post-transplant non-adherence ranges from 17%-40%[10–15]. A study showed that non-adherence assessed via self-report (likely underestimated) increased steadily from 6 months to 3 years post-LT and was present in about 1 of 5 LTRs[16]. Up to 25% of late acute rejection episodes (> 6 months post-LT and likely due to behavioral factors) are suspected to be caused by poor adherence[17,18]. Compounding this issue is the fact that often more intensive medical management is needed post-LT as immunosuppression leads to worsening hypertension (HTN), diabetes, and excessive weight gain[19–21]. LTRs must also engage in routine care with primary and specialty care, obtain follow-up testing, maintain up-to-date age-appropriate cancer screening, and vaccinations[22–24]. This creates a clinical challenge requiring multifaceted solutions.

We propose a multifaceted approach to enhance post-transplant adherence and care: The Technology-Enabled Strategies to promote Treatment adherence in Liver Transplant (TEST). This evidence-based and patient-centered strategy seeks to optimize the delivery of clinical care after LT.[25-27] Guided by our conceptual framework, we leverage widely available technology [28–35] (electronic health record (EHR), mobile devices) in a 'low touch' manner to support and track regimen use and activate appropriate transplant center clinical staff when specific problems are identified. The intervention is transplant-center-based given pre-existing resources and will leverage care partner support. Design was informed by patient and caregiver semi-structured interviews Herein we provide an overview of the TEST strategy and describe the methods and rationale for evaluating this approach in a randomized-controlled trial (RCT) funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Methods and Analysis:

Study Design and Aims

TEST is a 2-arm, prospective, patient-randomized, controlled trial at three large, diverse transplant centers with a goal of evaluating the effectiveness and implementation of the TEST strategy **(Figure 1)**. Specifically, our aims are to: 1) investigate the effectiveness of the TEST strategy to improve adherence to IS and non-IS medication regimens, functional health status, and health outcomes compared to usual care *(over the course of 18 months)*; 2) determine the fidelity of each component of the intervention over time and identify patient, care partner, clinician, or transplant center factors associated with optimal implementation; 3) assess the cost-effectiveness of TEST from a transplant center perspective.

Setting

The TEST trial is being conducted at the University of Pennsylvania, Northwestern University, and the University of Miami. The Penn Transplant Clinic (UPenn) is the largest multi-organ transplant center in the

Mid-Atlantic and ranks in the top 10 centers nationally with about 130-140 LTs annually. Northwestern Medicine Kovler Organ Transplant Center (Northwestern) is a large transplant center in the Midwest that performs multi-organ transplantation and living donor LT (80-100 per year). The Miami Transplant Institute (Miami) is one of the largest transplant centers in the U.S. based on transplant volumes with an average of 120-140 LTs performed annually.

Usual Care

Usual care refers to the normal standard clinical practices immediately post-transplant to the 18 months following. All 3 sites have similar protocols for follow-up. LTRs have lab values taken weekly for the first 8-10 weeks post-transplant, shifting to every 2-4 weeks for the next 3-4 months, then monthly to every 3 months thereafter depending on clinical needs. All sites follow a similar schedule of tapering clinic visits ranging from weekly in the first 4 weeks to every 2-4 weeks in months 4-6, every 3-6 months in months 7-12, and every 6 months in months 12-24. All sites assign each patient to a specific transplant coordinator, first paired with a transplant surgeon (first 3-6 months), and then a transplant hepatologist for the remainder of follow-up. Visit windows of +/- 30 days have been built in to allow scheduling flexibility. All patients and care partners receive standard medication teaching prior to hospital discharge and then ad hoc. No routine text message reminders about adherence are used in usual care.

TEST Intervention Arm

The TEST intervention is a technology-enabled strategy to routinely monitor regimen use, adherence, and persistence via a 'low touch', easy to use, online behavioral toolkit - Way to Health (W2H). Patients randomized to the intervention will have the option to also have their care partners receive the alerts, study messages, and monthly adherence assessments. The TEST strategy consists of several components designed to promote: 1) increased IS medication adherence, 2) routine surveillance of medication use and increased communication with transplant center staff between clinic visits, and 3) tailored clinical support based on individual challenges. The below components make up the TEST strategy:

1. **Two-Tiered Adherence Assessments & Clinician Alerts**- Patients and care partners will separately receive monthly SMS text or online assessments of adherence barriers through W2H **(Figure 2)**. We will deploy a two-tiered assessment to identify concerns among LTRs or care partners. The first tier will assess whether the patient is at risk for nonadherence (missed doses, missed timing, etc.) and the second tier will phenotype the nature of their concern as cognitive (memory issues, limited health literacy), psychological (depression, health activation, alcohol/substance use), medical (health status, acute concerns), regimen (dosing complexity, side effects), social (unmet tangible support needs, transportation), and economic (costs). At UPenn the W2H portal is automatically integrated into the electronic health record; at Miami and Northwestern clinical research coordinators will escalate the potential nonadherence alerts to the clinical team via email.
2. **Medication Reminders -** At enrollment, we will send the patient and designated care partner twice-daily medication reminders via the W2H portal. Patients and care partners will have the opportunity to reassess their needs at baseline and every 6 weeks to customize the timing of these messages (twice daily, daily, or opt out).
3. **Laboratory and Appointment Notifications -** The W2H portal will send pre-programmed text message laboratory and appointment reminders starting within 3 months of enrollment to Miami and Northwestern, UPenn already uses automated text-based appointment reminders as part of usual care. The rationale for delaying messages is based on feedback from transplant clinicians who commented that patients receive a lot of communication from LT centers as part of usual care and that additional messages from the study may be burdensome.

4. **Supplemental Self-Management Support** - To maintain long-term health, LTRs must engage in routine appointments with primary or specialty care, receive follow up imaging (e.g., bone density scans, CT/MRI scans to monitor for liver cancer recurrence, age-appropriate cancer screening, vaccinations). We will leverage the W2H platform to schedule text message or email health reminders following evidence-based guidelines to help promote long-term post-transplant health. A Recovery Support Program (RSP) will be available for LT recipients with moderate to high-risk pre-transplant alcohol use disorder (AUD), transplant for alcohol-associated hepatitis, or risk of alcohol misuse post-transplant as determined by treating psychiatrist/hepatologist at each site. The RSP consists of 12 education videos on topics related to alcohol recovery and sustained abstinence. A questionnaire will be sent out at varying time points during the study to assess the risk of relapse. Care partners will have the option to be assigned questionnaires to help with monitoring.

Participants

We plan to recruit 360 patients (n=120 per site) and up to 360 care partners at all sites over a 30-month period. Patients may enroll into the study without a care partner. Patient eligibility is as follows, 1) 18 years or older; 2) within 3 months of liver or liver/kidney transplant; 3) English- or Spanish-speaking; 4) home-dwelling; 5) owns a smart phone and is comfortable receiving text messages and/or accessing the internet via smart phone. Care partner eligibility includes: 1) 18 years or older; 2) English- or Spanish-speaking; 3) has access to a smart phone and is comfortable receiving text messages and/or accessing the internet via smart phone. Patients and/or care partners will be excluded if they have severe uncorrectable vision, hearing, or cognitive impairments that may impede study interviews.

Randomization and Blinding

Block randomization will occur within each site. Study patients will be allocated to either the TEST intervention group or usual care post LT in a 1:1 ratio stratified by site with a block size of 2. At each site, approximately 120 LTRs will be randomized via the W2H platform at the beginning of the baseline visit. Patients randomized to the TEST intervention arm will have the option to have their care partner receive alerts and study messages as well as complete monthly adherence forms for them. The intervention will not be blinded to research coordinators, however, investigators will be blinded to group allocation.

Human Subjects Protection and Clinical Trial Registration

The TEST Trial is using a single Institutional Review Board (sIRB) to oversee the study at all sites with the University of Pennsylvania IRB serving as the IRB of record. The trial is registered on clinicaltrials.gov [NCT05260268]. Research Coordinators (RCs) will obtain signed informed consent from all participants prior to their enrollment in the trial.

Recruitment and Data Collection

Recruitment will begin with RCs prescreening potentially eligible patients in the Electronic Health Record (EHR) at each site. Eligibility will be confirmed with the local site PI.

All potentially eligible participants and their care partners will be approached by the RC or site PI by telephone or in-person either prior to hospital discharge or during a post-transplant clinic visit. However, a patient can still enroll in the TEST Trial without a care partner, and care partners may change throughout the study. A baseline study visit will take place after obtaining informed consent and within 90 days post-transplant.

Follow-up study visits will be at 6, 12, and 18 months post-LT. Study data will be collected and managed using a REDCap (Research Electronic Data Capture) database hosted by the University of Pennsylvania Clinical Research Computing Unit (CRCU), the data management team.

Measurement

Patient Covariates

Study measures and timing of assessments are shown in **Table 1**. We will obtain sociodemographic information of both patients and care partners including but not limited to date of birth (DOB), age, address, sex assigned at birth, race, ethnicity, and employment status. Lifetime occupational complexity will be used to measure premorbid cognitive function[36,37]. Pre- and peri-operative transplant health status will be measured by MELD score at the time of LT[38], liver disease etiology, transplant hospitalization length of stay[39], discharge location[40], and medical comorbidities. Cognitive function will be measured with the Montreal Cognitive Assessment (MoCA)[41], the Animal Naming Test (ANT)[42], and visual acuity using the Rosenbaum Pocket Vision Screening Card utilizing PV Numbers™. We will use the Support with Medication Management Scale which assesses social support[43]. Healthcare navigation skills will be assessed using the "Liver Transplant Knowledge Questionnaire" (LTKQ), a novel survey designed by our study team that tests knowledge regarding immunosuppression timing and side effects. We will assess health literacy with the Newest Vital Sign (NVS)[44].

Care Partner Covariates

The same demographics measured in patients will also be obtained from care partners. Care partner self-efficacy will be assessed via the Caregiver Inventory (CGI)[45]. Preparedness of the care partner will be measured through the Caregiver Healthcare Task Difficulty and Preparedness Scales[46–48]. The nature and intensity of care provided will be assessed through information about the relationship of the care partner to the LTR, the number of hours of care provided per week, the care partner's duration of caregiving responsibilities, and travel time to the LTR's residence. Healthcare navigation skills will be assessed using the LTKQ, and care partner burden will be measured using the Zarit Burden Inventory, short form (ZBI-12)[49].

Outcomes

Medication Adherence. Adherence will be measured using: 1) 24-hour recall defined as patient self-report of how many pills and how often each medication was taken in the last 24 hours, 2) the Ask-12 scale that assesses general medication attitudes and beliefs[50], 3) regimen knowledge[6,51–55], and 4) a biologic measure using tacrolimus intra-patient variability. RCs will administer the 24 hour-recall where correct dosing will be measured as yes/no for each drug for the following domains: dose (number of pills), spacing (hours between doses), frequency (times per day), and total pills per day. General medication adherence will then be assessed with the brief Ask-12 scale that has 3 adherence related-subscales: medication behavior, health beliefs, and inconvenience/forgetfulness[50]. As part of the regimen knowledge assessment, we will ask the patient about the medical indication for each medication. Subsequently, understanding of proper dosing will be assessed by asking the patient to self-report the number of pills and spacing (hours apart) for each medication taken in the last 24 hours. Patient immunosuppression variability will be assessed with the tacrolimus coefficient of variation (COV) (100 x standard deviation/mean tacrolimus concentration), the medication level variability index (MLVI, standard deviation of at least three values), and tacrolimus time in the therapeutic range (TTR) [56–58]. Tacrolimus variability is associated with nonadherence (e.g. wrong or skipped dose, wrong drug timing, wrong laboratory timing), medication toxicity, kidney injury and poorer survival[56,59,60]. Calculations will be made at baseline, 6, 12 and 18 months using ≥3 levels obtained over the previous 3-6 months based on availability.

Health Related-Quality of Life: We will measure the health-related quality of life (HRQoL) of patients using the EQ-5D-5L. This survey assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with 5 questions, each with 5 possible answers, and, separately, self-rated health on a vertical visual analogue scale[61,62].

Functional Health Status: The functional health status of patients will be assessed at study visits using components of the Liver Frailty Index (LFI) and biometric measures from the most recent clinic visit. Objective measures of physical function will be assessed with the sit-to-stand, balance, and grip strength tests. Using these measures, we will calculate physical frailty with the validated liver frailty index (LFI) that combines grip strength, balance, and timed chair stand measures to classify patients' frailty severity[63].

Clinical Outcomes: We will assess 1) days hospitalized, 2) Days Alive and Out of Hospital (DAOH), 3) liver graft rejection, 4) liver graft failure, and 5) mortality. Days hospitalized and DAOH are both patient-centered, clinical outcomes validated for clinical trials[39,64,65]. Liver graft rejection, liver graft failure, and mortality will be assessed by liver biopsy and EHR, obtained as per usual care. Post-transplant infections will be assessed from the EHR using previous methodology developed by our group[6].

Chronic Disease Control: These data will be obtained at the end of the study from the EHR for the entire study period. We will examine longitudinal measures of chronic disease management including 1) office or hospital-based systolic/diastolic blood pressure, 2) hemoglobin A1c (HbA1c), 3) lipid profile (low-density lipoprotein cholesterol (LDL), triglycerides (TG)), and 4) kidney function measured by estimated rate (eGFR; mL/min/1.73m^2).

Acceptability, Feasibility: To evaluate the acceptability and feasibility of the TEST Trial, we will 1) conduct staff interviews, 2) obtain field notes from clinicians and research staff, and 3) conduct patient, caregiver, transplant clinician exit surveys to assess satisfaction with the intervention[51,66].

Fidelity: Fidelity will be measured through 1) completion of monthly assessments, 2) patient/care partner engagement with text messages, 3) percent of care alerts with clinical actions taken. Engagement with text messages will be analyzed by assessing the percent that result in appropriate EHR documentation and transplant center responses. Lastly, transplant center responses along with percent of laboratory, appointments, and self-management reminders appropriately deployed will be analyzed.

Costs: The cost of the TEST strategy will be conducted at UPenn LT and will be analyzed by investigating 1) W2H portal and implementation costs, 2) care partner, research staff, and clinical staff time, and 3) differences in LTRs' healthcare use during the trial. Measured costs will reflect the perspective of a transplant center considering adoption of the intervention, omitting costs related to research. Implementation costs include: evaluating the suitability of LTRs for the intervention; the technology platform and features needed for TEST, including the automatic text reminders for medications, labs, and visits; the monthly adherence assessment to be completed by LTRs and caregivers, and staff time. We will design the staff time measurement strategy in consultation with the transplant coordinators and will use time diaries, interviews, and direct observation if necessary. Because caregiving is essential to good LTR outcomes, and can impose substantial costs on caregivers, we will survey caregivers to measure their time spent and other burdens and expenditures. We will develop the survey based on items from the National Health and Aging Trends Study's National Study of Caregiving (NSOC)[67], to ask about the medical care and other tasks involved in caregiving, such as cleaning, shopping, and paying bills; any out-of-pocket expenditures, and the pressures on the rest of the caregiver's life. Finally, we will use the EHR to measure patients' medical care use in each study arm.

Data Analysis Plan

Better adherence to IS and non-IS regimens, greater treatment knowledge, and fewer dosing errors are the primary outcomes of interest for Aim 1. For each subject, we will have adherence measures at months 6, 12, and 18, representing adherence during follow-up intervals (0,3], (3,6], (6, 12] and (12,18], respectively. Adherence will be measured four different ways: a) 24-hour recall, b) Ask-12, c) regimen knowledge, and d) Tacrolimus variability. The ASK-12 questionnaire will be used to quantify barriers to adherence, with measurements at months 0, 6, 12 and 18. For each patient, the tacrolimus variability outcome will be represented by 4 time-interval specific Tac-CoV values modeled through a linear mixed model, including patient-specific random intercepts. For this outcome, the TEST and usual care groups will be compared through a linear mixed model with random patient-specific intercepts. Regimen knowledge will be modeled as a continuous outcome using the same approach. We will also carry out sensitivity analyses to further evaluate models: (a) we will repeat the analysis using different percentage thresholds to define pill count adherence (e.g. 90%) and will also evaluate adherence as a continuous measure. We will replace Tac-CoV with the Medication Level Variability Index (MLVI) [computed as tacrolimus SD] and will analyze the MLVI as a continuous and as a binary outcome (MLVI > 2). We will analyze tacrolimus TTR as an additional outcome.

Secondary outcomes of interest for Aim 1 include a) better health status and fewer hospitalization days as well as b) more optimal chronic disease control. Better health status and fewer hospitalization days will be measured through (i) days hospitalized, (ii) health-related quality of life, (iii) graft failure, (iv) graft rejection, and (v) infections. Days hospitalized will be modeled using a proportional rates model, which is essentially the recurrent event version of Cox regression. As a sensitivity analysis, we will model days-alive-out-of-hospital (DAOH) using semiparametric process regression methods developed by our team. EQ-5D-5L scores (available at months 0-3, 6, 12 and 18) will be modeled using a linear mixed model. Cox regression will be used to model graft failure; note that death will be included as a cause of graft failure. For graft rejection and infections, we will use the proportional rates model described above as both events may occur multiple times per patient. Linear mixed models will be fitted to the outcomes of blood pressure, HbA1c, eGFR, lipid levels.

Figure 3 shows power for each of the main analyses proposed in Aim 1. With a sample size of n=360, we have planned for a study dropout rate of 10% giving n=320. If drop-out exceeds 10%, we will use inverse probability of censoring weighting (IPCW), such that the weighted complete data represent the study sample.[68] Multiple imputation,[69] with 10 imputed data sets, will be used to impute missing values for covariates and outcomes with missingness >10% with PROC MI and PROC MIANALYZE (SAS, v9.4).

For Aim 2, we will determine the fidelity of each component of the intervention over time and investigate patient, care partner, provider, or transplant center factors associated with optimal implementation. Mixed methods will be employed using a convergent parallel design to obtain data on intervention implementation. We will capture 4 data sources: 1) W2H research dashboard, 2) EHR, 3) field notes, and 4) clinic staff. We will examine if receipt of W2H tools increased LTR adherence and impacted clinical outcomes. At 12- and 18-month interviews, a random sample of 25 patients and 25 care partners from the intervention arm at each site will be asked additional, semi-structured questions to explore 1) personal challenges with regimen adherence, 2) perceived value of the W2H portal tools, 3) unmet needs and acceptability of other tools and approaches to support medication use. Interviews will be audio-recorded and transcribed. Group or one-on-one interviews will be held with transplant staff to assess the intervention's impact on workflow.

Quantitative and qualitative findings pertaining to Aim 2 will be merged to answer 1) whether the intervention was implemented as planned (e.g. fidelity), and 2) whether, from a user-perspective, the interventions require modification and how. In this approach, both analyses are conducted separately and merged for side-by-side data comparisons. For qualitative data, we will review and explore any transcribed patient interviews and clinic staff discussions using content and ethnographic analysis. Predetermined

categories will organize feedback from all users: patient, care partner, clinic/health system. Within each of these categories we will use a predetermined coding approach to quantify the frequency of two subcategories: facilitating factors, and impeding factors. The effect of patient characteristics on fidelity will be quantified using mixed logistic regression; we will fit separate models for patients and care partners. With respect to providers, fidelity will be represented by the fractions of alerts that trigger a clinical response. Response probability will be modeled through mixed logistic regression where, for each provider, the number of 'trials' and 'successes' will be set to the number of alerts and responses thereto, respectively. We will assess the relationship between the intervention effect (i.e., intervention versus usual care) and fidelity through interaction terms. For each time point (e.g., 12 months), we will have a covariate for survey completion fraction during the preceding follow-up interval (e.g., 5/6 surveys completed for months 7 to 12).

For Aim 3, we will assess the costs and cost-effectiveness of the TEST intervention from a transplant center perspective. We will evaluate the cost-effectiveness of the TEST intervention, relating implementation costs to any changes in health-related quality of life, as measured by the EQ-5D-5L. We will also relate implementation costs to medication adherence and days hospitalized, the primary and secondary trial outcomes. The costing and cost-effectiveness analyses will be summarized in the form of center costs per LTR (with detail by type of cost) and in incremental cost effectiveness ratios (ICERs) that show the difference in implementation costs between intervention and control arms divided by the difference in health outcome (e.g., EQ-5D-5L). One-way and multi-way sensitivity analyses will be conducted to determine the key drivers behind costs and cost-effectiveness ratios, with particular attention to factors such as attrition, that may differ between the trial and ordinary practice.

Data:

The study contains potentially sensitive transplant outcomes data that will be made available upon request.

Ethics and Dissemination:

The University of Pennsylvania Review Board has approved the study as the single IRB (sIRB) of record (protocol # 849575). All protocol changes will be communicated and approved by the sIRB. An external Data Safety and Monitoring Board (DSMB) will serve as a safety monitoring entity for this study. The DSMB will include a biostatistician, and 3 researchers with relevant expertise. This is a minimal risk study with no interim analyses or stopping rules. Any study related serious adverse events will be reported to the site PI and study PI within 3 days and to the DSMB, IRB, sponsor (NIDDK) in writing within 7 days of investigators becoming aware. To ensure data confidentiality records will be stored in a secured RedCAP database environment. Final peer-reviewed manuscripts that arise from this proposal will be submitted to PubMed Central for digital archiving. Our informed consent document for this clinical trial will includes a statement acknowledging the posting of eligibility criteria and study information on clinicaltrials.gov, as well as the subsequent results.

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Figure legends.

Figure 1. Description of TEST Intervention
Figure 2. Categories of Two-Tiered Adherence Assessment
Figure 3. Power Analyses

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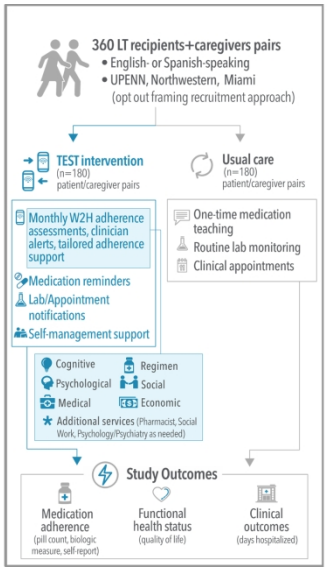
Competing Interest Statement
MS reports additional grants from NIH/NIDDK and Grifols, SA.

Table 1. Study measures and timing of assessments

		Interview Timepoint			
Variable	**Instrument(s) or Measure(s)**	**BL (Day 0-90 +30)**	**6M (Day 180 +/- 30)**	**12M (Day 360 +/- 30)**	**18M (Day 540 +/- 30)**
Informed Consent	**Informed Consent**	X			
Sociodemographics	**Date of Birth**	X			
	Age	X			
	Address	X			
	Sex Assigned at Birth	X			
	Gender Identity	X			
	Race	X			
	Ethnicity	X			
	Marital Status	X			
	Employment	X			
	Lifetime Occupational Complexity	X			
Pre and Peri-Operative Transplant Health Status	**MELD score at time of LT**	X			
	Liver Disease Etiology	X			
	Transplant Length of Stay	X			
	Discharge location	X			
	Medical Comorbidities	X			
Cognitive Status Measurement	**Montreal Cognitive Assessment (MoCA)**	X	X		X
	Animal Naming Test (ANT)	X	X		X
	Rosenbaum Visual Acuity	X	X		X
Social Support	**Modified Support with Medication Management Scale (SMMS)**	X	X	X	X

Healthcare Navigation Skills	**Liver Transplant Knowledge Questionnaire (LTKQ)**	X	X	X	X
Health Literacy	**Newest Vital Sign (NVS)**	X			
Medication Adherence	**24-Hour Recall, Regimen Knowledge**	X	X	X	X
	Tacrolimus Lab Values	X	X	X	X
	ASK-12	X	X	X	X
Health-Related Quality of Life	**EQ-5D-5L**	X	X	X	X
	Alcohol, Tobacco, and Drugs Survey	X	X	X	X
Functional Health Status	**Grip Strength**	X	X	X	X
	30 Second Chair Stand	X	X	X	X
	Balance Test	X	X	X	X
	Liver Frailty Index Calculation	X	X	X	X
	Most Recent Height, Weight, and BP	X	X	X	X
Chronic Disease Control	**Lipids (LDL, TG) and eGFR**	X	X	X	X
	HBA1C	X	X	X	X

Care Partner Study Measures and Outcomes		**Interview Timepoint**			
Variable	**Instrument(s) or Measure(s)**	**BL (Day 0-90 +30)**	**6M (Day 180 +/- 30)**	**12M (Day 360 +/- 30)**	**18M (Day 540 +/- 30)**
Informed Consent	**Informed Consent**	X			
Sociodemographics	**Date of Birth**	X			
	Age	X			
	Address	X			
	Sex Assigned at Birth	X			
	Gender Identity	X			
	Race	X			
	Ethnicity	X			
	Marital Status	X			
	Employment	X			
	Lifetime Occupational Complexity	X			
Self-Efficacy	**Caregiver Inventory (CGI)**	X	X	X	X
Preparedness	**Modified Caregiver Healthcare Task Difficulty and Preparedness Scale**	X	X	X	X
Nature and Intensity of Care	**Relationship to Patient**	X	X	X	X
	Hours of Care Provided	X	X	X	X
	Duration of Responsibility	X	X	X	X
	Nature of Assistance Provided	X	X	X	X
Healthcare Navigation Skills	**Liver Transplant Knowledge Questionnaire (LTKQ)**	X	X	X	X
Care Partner Burden	**Short Form Zarit Burden Interview (ZBI-12)**	X	X	X	X
Physical & General Health	**Physical & General Health Questionnaire**	X	X	X	X



Description of TEST Intervention

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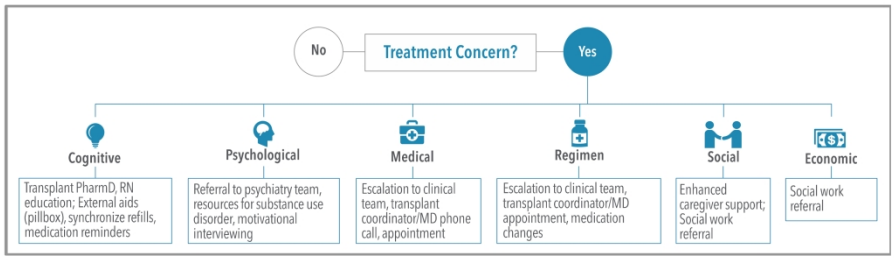

Categories of Two-Tiered Adherence Assessment

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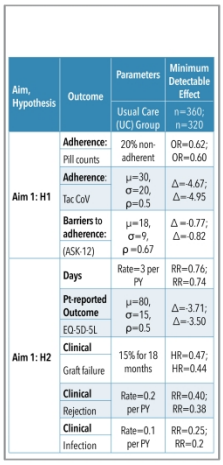

Aim, Hypothesis	Outcome	Parameters	Minimum Detectable Effect
		Usual Care (UC) Group	n=360; n=320
Aim 1: H1	Adherence: Pill counts	20% non-adherent	OR=0.62; OR=0.60
	Adherence: Tac CoV	μ=30, σ=20, ρ=0.5	Δ=-4.67; Δ=-4.95
	Barriers to adherence: (ASK-12)	μ=18, σ=9, ρ=0.67	Δ=-0.77; Δ=-0.82
Aim 1: H2	Days	Rate=3 per PY	RR=0.76; RR=0.74
	Pt-reported Outcome EQ-5D-5L	μ=80, σ=15, ρ=0.5	Δ=-3.71; Δ=-3.50
	Clinical Graft failure	15% for 18 months	HR=0.47; HR=0.44
	Clinical Rejection	Rate=0.2 per PY	RR=0.40; RR=0.38
	Clinical Infection	Rate=0.1 per PY	RR=0.25; RR=0.2

Power analyses

338x190mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2, 14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	6

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-9
Objectives	#7	Specific objectives or hypotheses	7-8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	3-5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14, 15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5-6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	5

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-6

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8-9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	9

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5-6
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	1, 14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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A Patient-Randomized Controlled Trial of Technology Enabled Strategies to promote Treatment adherence in Liver Transplantation: Rationale and Design of the TEST Trial

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FDA Patient-Randomized Controlled Trial of Technology Enabled Strategies to promote Treatment adherence in Liver Transplantation: Rationale and Design of the TEST Trial

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Abstract

Background and Aims: Liver transplantation is a life-saving procedure for end-stage liver disease. However, post-transplant medication regimens are complex and non-adherence is common. Post-transplant medication non-adherence is associated with graft rejection, which can have long-term adverse consequences. Transplant centers are equipped with clinical staff that monitor patients post-transplant; however, digital health tools and proactive immunosuppression adherence monitoring has potential to improve outcomes.

Methods and Analysis: This is a patient-randomized prospective clinical trial at 3 transplant centers in the Northeast, Midwest, and South to investigate the effects of a remotely-administered adherence program compared to usual care. The program monitors potential non-adherence largely levering text message prompts and phenotypes the nature of the non-adhere as cognitive, psychological, medical, social, or economic. Additional reminders for medications, clinical appointments and routine self-management support are incorporated to promote adherence to the entire medical regimen. The primary study outcome is medication adherence via 24-hour recall; secondary outcomes include additional medication adherence (ASK-12 self-reported scale, regimen knowledge scales, tacrolimus values), quality of life, functional health status, and clinical outcomes (e.g. days hospitalized). Study implementation, acceptability, feasibility, costs and potential cost-effectiveness will also be evaluated.

Ethics and Dissemination: The University of Pennsylvania Review Board has approved the study as the single IRB of record (protocol # 849575, V1.4). Results will be published in peer-reviewed journals and summaries will be provided to study funders.

Registration: NCT05260268

Article Summary:

Strengths and limitations of this study

- This is a multi-center trial conducted in English and Spanish that includes de-novo liver and liver/kidney transplant recipients.
- We will assess efficacy as well as implementation outcomes and costs.
- Limitations include that clinical trial participants may be more engaged than average.
- Findings may not apply to settings that do not use electronic health records or to patients who do not own or use cellphones.

Introduction

Liver transplant (LT), while providing a substantial survival benefit for decompensated liver disease, is a costly and limited resource[1–4]. With advances in surgical techniques and immunosuppression (IS), 5-year post-transplant survival exceeds 70%[5]. However, liver transplant recipients (LTRs) manage complex immunosuppression regimens to maintain graft function. LTRs must navigate complex health-systems, adhere to lifestyle changes, clinical monitoring, and take multiple medications with potential side effects and frequent dosing changes[6,7], all requiring robust health literacy and self-management skills. LTRs take on average 11 medications and 39% report a medication change within the past 30 days[6]. Additionally, 38% of LT candidates have inadequate health literacy[8], and lower health literacy is associated with poor treatment knowledge and higher IS nonadherence[6,9].

Post-transplant non-adherence ranges from 17%-40%[10–15]. A study showed that non-adherence assessed via self-report (likely underestimated) increased steadily from 6 months to 3 years post-LT and was present in about 1 of 5 LTRs[16]. Up to 25% of late acute rejection episodes (> 6 months post-LT and likely due to behavioral factors) are suspected to be caused by poor adherence[17,18]. Compounding this issue is the fact that often more intensive medical management is needed post-LT as immunosuppression leads to worsening hypertension (HTN), diabetes, and excessive weight gain[19–21]. LTRs must also engage in routine care with primary and specialty care, obtain follow-up testing, maintain up-to-date age-appropriate cancer screening, and vaccinations[22–24]. This creates a clinical challenge requiring multifaceted solutions[25-27].

We propose a multifaceted approach to enhance post-transplant adherence and care: The Technology-Enabled Strategies to promote Treatment adherence in Liver Transplant (TEST). Guided by our conceptual framework, we leverage widely available technology [28–35] (electronic health record (EHR), mobile devices) in a 'low touch' manner to support and track regimen use and activate appropriate transplant center clinical staff when specific problems are identified. Herein we provide an overview of the TEST strategy and describe the methods and rationale for evaluating this approach in a randomized-controlled trial (RCT) funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Methods and Analysis:

Study Design and Aims

TEST is a 2-arm, prospective, patient-randomized, controlled trial at three large, diverse transplant centers with a goal of evaluating the effectiveness and implementation of the TEST strategy **(Figure 1)**. Specifically, our aims are to: 1) investigate the effectiveness of the TEST strategy to improve adherence to IS and non-IS medication regimens, functional health status, and health outcomes compared to usual care *(over the course of 18 months)*; 2) determine the fidelity of each component of the intervention over time and identify patient, care partner, clinician, or transplant center factors associated with optimal implementation; 3) assess the cost-effectiveness of TEST from a transplant center perspective.

Patient and Public Involvement

There was no patient or public involvement in the design of this study. However, study results will be disseminated to trial participants and the Liver Transplant Virtual Patient Support Group at the University of Pennsylvania.

Setting

The TEST trial is being conducted at the University of Pennsylvania, Northwestern University, and the University of Miami from May of 2022 to April 2027. The Penn Transplant Clinic (UPenn) is the largest multi-organ transplant center in the Mid-Atlantic and ranks in the top 10 centers nationally with about 130-140 LTs annually. Northwestern Medicine Kovler Organ Transplant Center (Northwestern) is a large transplant center in the Midwest that performs multi-organ transplantation and living donor LT (80-100 per year). The Miami Transplant Institute (Miami) is one of the largest transplant centers in the U.S. based on transplant volumes with an average of 120-140 LTs performed annually.

Usual Care

Usual care refers to the normal standard clinical practices immediately post-transplant to the 18 months following. All 3 sites have similar protocols for follow-up. LTRs have lab values taken weekly for the first 8-10 weeks post-transplant, shifting to every 2-4 weeks for the next 3-4 months, then monthly to every 3 months thereafter depending on clinical needs. All sites follow a similar schedule of tapering clinic visits ranging from weekly in the first 4 weeks to every 2-4 weeks in months 4-6, every 3-6 months in months 7-12, and every 6 months in months 12-24. All sites assign each patient to a specific transplant coordinator, first paired with a transplant surgeon (first 3-6 months), and then a transplant hepatologist for the remainder of follow-up. Visit windows of +/- 30 days have been built in to allow scheduling flexibility. All patients and care partners receive standard medication teaching prior to hospital discharge and then ad hoc. No routine text message reminders about adherence are used in usual care.

TEST Intervention Arm

The TEST intervention is a technology-enabled strategy to routinely monitor regimen use, adherence, and persistence via a 'low touch', easy to use, online behavioral toolkit - Way to Health (W2H). Patients randomized to the intervention will have the option to also have their care partners receive the alerts, study messages, and monthly adherence assessments. The TEST strategy consists of several components designed to promote: 1) increased IS medication adherence, 2) routine surveillance of medication use and increased communication with transplant center staff between clinic visits, and 3) tailored clinical support based on individual challenges. The below components make up the TEST strategy:

1. **Two-Tiered Adherence Assessments & Clinician Alerts**- Patients and care partners will separately receive monthly SMS text or online assessments of adherence barriers through W2H **(Figure 2)**. We will deploy a two-tiered assessment to identify concerns among LTRs or care partners. The first tier will assess whether the patient is at risk for nonadherence (missed doses, missed timing, etc.) and the second tier will phenotype the nature of their concern as cognitive (memory issues, limited health literacy), psychological (depression, health activation, alcohol/substance use), medical (health status, acute concerns), regimen (dosing complexity, side effects), social (unmet tangible support needs, transportation), and economic (costs). At UPenn the W2H portal is automatically integrated into the electronic health record; at Miami and Northwestern clinical research coordinators will escalate the potential nonadherence alerts to the clinical team via email.
2. **Medication Reminders -** At enrollment, we will send the patient and designated care partner twice-daily medication reminders via the W2H portal. Patients and care partners will have the opportunity to reassess their needs at baseline and every 6 weeks to customize the timing of these messages (twice daily, daily, or opt out).

3. **Laboratory and Appointment Notifications -** The W2H portal will send pre-programmed text message laboratory and appointment reminders starting within 3 months of enrollment to Miami and Northwestern, UPenn already uses automated text-based appointment reminders as part of usual care. The rationale for delaying messages is based on feedback from transplant clinicians who commented that patients receive a lot of communication from LT centers as part of usual care and that additional messages from the study may be burdensome.
4. **Supplemental Self-Management Support** - To maintain long-term health, LTRs must engage in routine appointments with primary or specialty care, receive follow up imaging (e.g., bone density scans, CT/MRI scans to monitor for liver cancer recurrence, age-appropriate cancer screening, vaccinations). We will leverage the W2H platform to schedule text message or email health reminders following evidence-based guidelines to help promote long-term post-transplant health. A Recovery Support Program (RSP) will be available for LT recipients with moderate to high-risk pre-transplant alcohol use disorder (AUD), transplant for alcohol-associated hepatitis, or risk of alcohol misuse post-transplant as determined by treating psychiatrist/hepatologist at each site. The RSP consists of 12 education videos on topics related to alcohol recovery and sustained abstinence. A questionnaire will be sent out at varying time points during the study to assess the risk of relapse. Care partners will have the option to be assigned questionnaires to help with monitoring.

Participants

We plan to recruit 360 patients (n=120 per site) and up to 360 care partners at all sites over a 30-month period. Patients may enroll into the study without a care partner. Patient eligibility is as follows, 1) 18 years or older; 2) within 3 months of liver or liver/kidney transplant; 3) English- or Spanish-speaking; 4) home-dwelling; 5) owns a smart phone and is comfortable receiving text messages and/or accessing the internet via smart phone. Care partner eligibility includes: 1) 18 years or older; 2) English- or Spanish-speaking; 3) has access to a smart phone and is comfortable receiving text messages and/or accessing the internet via smart phone. Patients and/or care partners will be excluded if they have severe uncorrectable vision, hearing, or cognitive impairments that may impede study interviews.

Randomization and Blinding

Block randomization will occur within each site. Study patients will be allocated to either the TEST intervention group or usual care post LT in a 1:1 ratio stratified by site with a block size of 2. At each site, approximately 120 LTRs will be randomized via the W2H platform at the beginning of the baseline visit. Patients randomized to the TEST intervention arm will have the option to have their care partner receive alerts and study messages as well as complete monthly adherence forms for them. The intervention will not be blinded to research coordinators, however, investigators will be blinded to group allocation.

Human Subjects Protection and Clinical Trial Registration

The TEST Trial is using a single Institutional Review Board (sIRB) to oversee the study at all sites with the University of Pennsylvania IRB serving as the IRB of record. The trial is registered on clinicaltrials.gov [NCT05260268]. Research Coordinators (RCs) will obtain signed informed consent from all participants prior to their enrollment in the trial (see attached in Supplemental material).

Recruitment and Data Collection

Recruitment will begin with RCs prescreening potentially eligible patients in the Electronic Health Record (EHR) at each site. Eligibility will be confirmed with the local site PI.

All potentially eligible participants and their care partners will be approached by the RC or site PI by telephone or in-person either prior to hospital discharge or during a post-transplant clinic visit. However, a patient can still enroll in the TEST Trial without a care partner, and care partners may change throughout the study. A baseline study visit will take place after obtaining informed consent and within 90 days post-transplant. Follow-up study visits will be at 6, 12, and 18 months post-LT. Study data will be collected and managed using a REDCap (Research Electronic Data Capture) database hosted by the University of Pennsylvania Clinical Research Computing Unit (CRCU), the data management team.

Measurement

Patient Covariates

Study measures and timing of assessments are shown in **Table 1**. We will obtain sociodemographic information of both patients and care partners including but not limited to date of birth (DOB), age, address, sex assigned at birth, race, ethnicity, and employment status. Lifetime occupational complexity will be used to measure premorbid cognitive function[36,37]. Pre- and peri-operative transplant health status will be measured by MELD score at the time of LT[38], liver disease etiology, transplant hospitalization length of stay[39], discharge location[40], and medical comorbidities. Cognitive function will be measured with the Montreal Cognitive Assessment (MoCA)[41], the Animal Naming Test (ANT)[42], and visual acuity using the Rosenbaum Pocket Vision Screening Card utilizing PV Numbers™. We will use the Support with Medication Management Scale which assesses social support[43]. Healthcare navigation skills will be assessed using the "Liver Transplant Knowledge Questionnaire" (LTKQ), a novel survey designed by our study team that tests knowledge regarding immunosuppression timing and side effects. We will assess health literacy with the Newest Vital Sign (NVS)[44].

Care Partner Covariates

The same demographics measured in patients will also be obtained from care partners. Care partner self-efficacy will be assessed via the Caregiver Inventory (CGI)[45]. Preparedness of the care partner will be measured through the Caregiver Healthcare Task Difficulty and Preparedness Scales[46–48]. The nature and intensity of care provided will be assessed through information about the relationship of the care partner to the LTR, the number of hours of care provided per week, the care partner's duration of caregiving responsibilities, and travel time to the LTR's residence. Healthcare navigation skills will be assessed using the LTKQ, and care partner burden will be measured using the Zarit Burden Inventory, short form (ZBI-12)[49].

Outcomes

Medication Adherence. The primary adherence outcome will be measured using 24-hour recall defined as patient self-report of how many pills and how often each medication was taken in the last 24 hours. Additional secondary adherence measures include 2) the Ask-12 scale that assesses general medication attitudes and beliefs[50], 3) regimen knowledge[6,51–55], and 4) a biologic measure using tacrolimus intra-patient variability. RCs will administer the 24 hour-recall where correct dosing will be measured as yes/no for each drug for the following domains: dose (number of pills), spacing (hours between doses), frequency (times per day), and total pills per day. General medication adherence will then be assessed with the brief Ask-12 scale that has 3 adherence related-subscales: medication behavior, health beliefs, and inconvenience/forgetfulness[50]. As part of the regimen knowledge assessment, we will ask the patient about the medical indication for each medication. Subsequently, understanding of proper dosing will be assessed by asking the patient to self-report the number of pills and spacing (hours apart) for each medication taken in the last 24 hours. Patient

immunosuppression variability will be assessed with the tacrolimus coefficient of variation (COV) (100 x standard deviation/mean tacrolimus concentration), the medication level variability index (MLVI, standard deviation of at least three values), and tacrolimus time in the therapeutic range (TTR) [56–58]. Tacrolimus variability is associated with nonadherence (e.g. wrong or skipped dose, wrong drug timing, wrong laboratory timing), medication toxicity, kidney injury and poorer survival[56,59,60]. Calculations will be made at baseline, 6, 12 and 18 months using ≥3 levels obtained over the previous 3-6 months based on availability.

Health Related-Quality of Life: We will measure the health-related quality of life (HRQoL) of patients using the EQ-5D-5L. This survey assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with 5 questions, each with 5 possible answers, and, separately, self-rated health on a vertical visual analogue scale[61,62].

Functional Health Status: The functional health status of patients will be assessed at study visits using components of the Liver Frailty Index (LFI) as well as the timed and go test. Objective measures of physical function will be assessed with the sit-to-stand, balance, and grip strength tests. Using these measures, we will calculate physical frailty with the validated liver frailty index (LFI) that combines grip strength, balance, and timed chair stand measures to classify patients' frailty severity[63].

Clinical Outcomes: We will assess 1) days hospitalized, 2) Days Alive and Out of Hospital (DAOH), 3) liver graft outcomes: liver graft rejection and liver graft failure, and 5) mortality. Days hospitalized and DAOH are both patient-centered, clinical outcomes validated for clinical trials[39,64,65]. Liver graft rejection, liver graft failure, and mortality will be assessed by liver biopsy and EHR, obtained as per usual care. Post-transplant infections will be assessed from the EHR using previous methodology developed by our group[6].

Chronic Disease Control: These data will be obtained at the end of the study from the EHR for the entire study period. We will examine longitudinal measures of chronic disease management including 1) office or hospital-based systolic/diastolic blood pressure, 2) hemoglobin A1c (HbA1c), 3) lipid profile (low-density lipoprotein cholesterol (LDL), triglycerides (TG)), and 4) kidney function measured by estimated rate (eGFR; mL/min/1.73m^2).

Acceptability, Feasibility: To evaluate the acceptability and feasibility of the TEST Trial, we will 1) conduct staff interviews, 2) obtain field notes from clinicians and research staff, and 3) conduct patient, caregiver, transplant clinician exit surveys to assess satisfaction with the intervention[51,66].

Fidelity: Fidelity will be measured through 1) completion of monthly assessments, 2) patient/care partner engagement with text messages, 3) percent of care alerts with clinical actions taken. Engagement with text messages will be analyzed by assessing the percent that result in appropriate EHR documentation and transplant center responses. Lastly, transplant center responses along with percent of laboratory, appointments, and self-management reminders appropriately deployed will be analyzed.

Costs: The cost of the TEST strategy will be conducted at UPenn LT and will be analyzed by investigating 1) W2H portal and implementation costs, 2) care partner, research staff, and clinical staff time, and 3) differences in LTRs' healthcare use during the trial. Measured costs will reflect the perspective of a transplant center considering adoption of the intervention, omitting costs related to research. Implementation costs include: evaluating the suitability of LTRs for the intervention; the technology platform and features needed for TEST, including the automatic text reminders for medications, labs, and visits; the monthly adherence assessment to be completed by LTRs and caregivers, and staff time. We will design the staff time measurement strategy in consultation with the transplant coordinators and will use time diaries, interviews, and direct observation if necessary. Because caregiving is essential to good LTR outcomes, and can impose

substantial costs on caregivers, we will survey caregivers to measure their time spent and other burdens and expenditures. We will develop the survey based on items from the National Health and Aging Trends Study's National Study of Caregiving (NSOC)[67], to ask about the medical care and other tasks involved in caregiving, such as cleaning, shopping, and paying bills; any out-of-pocket expenditures, and the pressures on the rest of the caregiver's life. Finally, we will use the EHR to measure patients' medical care use in each study arm.

Data Analysis Plan

Better adherence to IS and non-IS regimens, greater treatment knowledge, and fewer dosing errors are the primary outcomes of interest for Aim 1. For each subject, we will have adherence measures at months 6, 12, and 18, representing adherence during follow-up intervals (0,3], (3,6], (6, 12] and (12,18], respectively. Adherence will be measured four different ways: a) 24-hour recall, b) Ask-12, c) regimen knowledge, and d) Tacrolimus variability. The ASK-12 questionnaire will be used to quantify barriers to adherence, with measurements at months 0, 6, 12 and 18. For each patient, the tacrolimus variability outcome will be represented by 4 time-interval specific Tac-CoV values modeled through a linear mixed model, including patient-specific random intercepts. For this outcome, the TEST and usual care groups will be compared through a linear mixed model with random patient-specific intercepts. Regimen knowledge will be modeled as a continuous outcome using the same approach. We will also carry out sensitivity analyses to further evaluate models: (a) we will repeat the analysis using different percentage thresholds to define pill count adherence (e.g. 90%) and will also evaluate adherence as a continuous measure. We will replace Tac-CoV with the Medication Level Variability Index (MLVI) [computed as tacrolimus SD] and will analyze the MLVI as a continuous and as a binary outcome (MLVI > 2). We will analyze tacrolimus TTR as an additional outcome.

Secondary outcomes of interest for Aim 1 include a) better health status and fewer hospitalization days as well as b) more optimal chronic disease control. Better health status and fewer hospitalization days will be measured through (i) days hospitalized, (ii) health-related quality of life, (iii) graft failure, (iv) graft rejection, and (v) infections. Days hospitalized will be modeled using a proportional rates model, which is essentially the recurrent event version of Cox regression. EQ-5D-5L scores (available at months 0-3, 6, 12 and 18) will be modeled using a linear mixed model. Cox regression will be used to model graft failure. For graft rejection and infections, we will use the proportional rates model described above as both events may occur multiple times per patient. Linear mixed models will be fitted to the outcomes of blood pressure, HbA1c, eGFR, lipid levels.

Figure 3 shows power for each of the main analyses proposed in Aim 1. With a sample size of n=360, we have planned for a study dropout rate of 10% giving n=320. If drop-out exceeds 10%, we will use inverse probability of censoring weighting (IPCW), such that the weighted complete data represent the study sample.[68] Multiple imputation,[69] with 10 imputed data sets, will be used to impute missing values for covariates and outcomes with missingness >10% with PROC MI and PROC MIANALYZE (SAS, v9.4).

For Aim 2, we will determine the fidelity of each component of the intervention over time and investigate patient, care partner, provider, or transplant center factors associated with optimal implementation. Mixed methods will be employed using a convergent parallel design to obtain data on intervention implementation. We will capture 4 data sources: 1) W2H research dashboard, 2) EHR, 3) field notes, and 4) clinic staff. We will examine if receipt of W2H tools increased LTR adherence and impacted clinical outcomes. At 12- and 18-month interviews, a random sample of 25 patients and 25 care partners from the intervention arm at each site will be asked additional, semi-structured questions to explore 1) personal challenges with regimen adherence, 2) perceived value of the W2H portal tools, 3) unmet needs and acceptability of other tools and approaches to support medication use. Interviews will be audio-recorded and transcribed. Group or one-on-one interviews will be held with transplant staff to assess the intervention's impact on workflow.

Quantitative and qualitative findings pertaining to Aim 2 will be merged to answer 1) whether the intervention was implemented as planned (e.g. fidelity), and 2) whether, from a user-perspective, the interventions require modification and how. In this approach, both analyses are conducted separately and merged for side-by-side data comparisons. For qualitative data, we will review and explore any transcribed patient interviews and clinic staff discussions using content and ethnographic analysis. The effect of patient characteristics on fidelity will be quantified using mixed logistic regression; we will fit separate models for patients and care partners. With respect to providers, fidelity will be represented by the fractions of alerts that trigger a clinical response. Response probability will be modeled through mixed logistic regression where, for each provider, the number of 'trials' and 'successes' will be set to the number of alerts and responses thereto, respectively. We will assess the relationship between the intervention effect (i.e., intervention versus usual care) and fidelity through interaction terms. For each time point (e.g., 12 months), we will have a covariate for survey completion fraction during the preceding follow-up interval (e.g., 5/6 surveys completed for months 7 to 12).

For Aim 3, we will assess the costs and cost-effectiveness of the TEST intervention from a transplant center perspective. We will evaluate the cost-effectiveness of the TEST intervention, relating implementation costs to any changes in health-related quality of life, as measured by the EQ-5D-5L. We will also relate implementation costs to medication adherence and days hospitalized, the primary and secondary trial outcomes. The costing and cost-effectiveness analyses will be summarized in the form of center costs per LTR (with detail by type of cost) and in incremental cost effectiveness ratios (ICERs) that show the difference in implementation costs between intervention and control arms divided by the difference in health outcome (e.g., EQ-5D-5L). One-way and multi-way sensitivity analyses will be conducted to determine the key drivers behind costs and cost-effectiveness ratios, with particular attention to factors such as attrition, that may differ between the trial and ordinary practice.

Data:
The study contains potentially sensitive transplant outcomes data that will be made available upon request.

Ethics and Dissemination:
The University of Pennsylvania Review Board has approved the study as the single IRB (sIRB) of record (protocol # 849575). All protocol changes will be communicated and approved by the sIRB. An external Data Safety and Monitoring Board (DSMB) will serve as a safety monitoring entity for this study. The DSMB will include a biostatistician, and 3 researchers with relevant expertise. This is a minimal risk study with no interim analyses or stopping rules. Any study related serious adverse events will be reported to the site PI and study PI within 3 days and to the DSMB, IRB, sponsor (NIDDK) in writing within 7 days of investigators becoming aware. To ensure data confidentiality records will be stored in a secured RedCAP database environment. Our informed consent document for this clinical trial will includes a statement acknowledging the posting of eligibility criteria and study information on clinicaltrials.gov, as well as the subsequent results.

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Figure legends.

Figure 1. Description of TEST Intervention
Figure 2. Categories of Two-Tiered Adherence Assessment
Figure 3. Power Analyses

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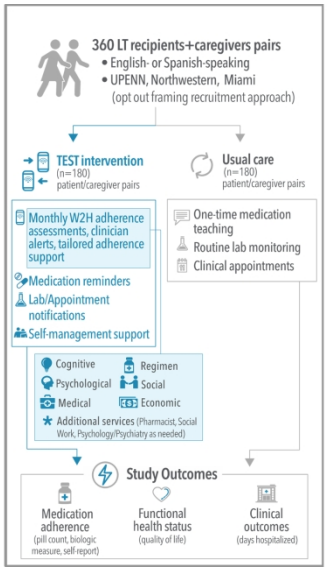
Competing Interest Statement
MS reports additional grants from NIH/NIDDK and Grifols, SA.

Table 1. Study measures and timing of assessments

		Interview Timepoint			
Variable	**Instrument(s) or Measure(s)**	**BL (Day 0-90 +30)**	**6M (Day 180 +/- 30)**	**12M (Day 360 +/- 30)**	**18M (Day 540 +/- 30)**
Informed Consent	**Informed Consent**	X			
Sociodemographics	**Date of Birth**	X			
	Age	X			
	Address	X			
	Sex Assigned at Birth	X			
	Gender Identity	X			
	Race	X			
	Ethnicity	X			
	Marital Status	X			
	Employment	X			
	Lifetime Occupational Complexity	X			
Pre and Peri-Operative Transplant Health Status	**MELD score at time of LT**	X			
	Liver Disease Etiology	X			
	Transplant Length of Stay	X			
	Discharge location	X			
	Medical Comorbidities	X			
Cognitive Status Measurement	**Montreal Cognitive Assessment (MoCA)**	X	X		X
	Animal Naming Test (ANT)	X	X		X
	Rosenbaum Visual Acuity	X	X		X
Social Support	**Modified Support with Medication Management Scale (SMMS)**	X	X	X	X
Healthcare Navigation Skills	**Liver Transplant Knowledge Questionnaire (LTKQ)**	X	X	X	X
Health Literacy	**Newest Vital Sign (NVS)**	X			
Medication Adherence	**24-Hour Recall, Regimen Knowledge**	X	X	X	X
	Tacrolimus Lab Values	X	X	X	X

	ASK-12	X	X	X	X
Health-Related Quality of Life	**EQ-5D-5L**	X	X	X	X
	Alcohol, Tobacco, and Drugs Survey	X	X	X	X
Functional Health Status	**Grip Strength**	X	X	X	X
	30 Second Chair Stand	X	X	X	X
	Balance Test	X	X	X	X
	Liver Frailty Index Calculation	X	X	X	X
	Most Recent Height, Weight, and BP	X	X	X	X
Chronic Disease Control	**Lipids (LDL, TG) and eGFR**	X	X	X	X
	HBA1C	X	X	X	X

Care Partner Study Measures and Outcomes		**Interview Timepoint**			
Variable	**Instrument(s) or Measure(s)**	**BL (Day 0-90 +30)**	**6M (Day 180 +/- 30)**	**12M (Day 360 +/- 30)**	**18M (Day 540 +/- 30)**
Informed Consent	**Informed Consent**	X			
Sociodemographics	**Date of Birth**	X			
	Age	X			
	Address	X			
	Sex Assigned at Birth	X			
	Gender Identity	X			
	Race	X			
	Ethnicity	X			
	Marital Status	X			
	Employment	X			
	Lifetime Occupational Complexity	X			
Self-Efficacy	**Caregiver Inventory (CGI)**	X	X	X	X
Preparedness	**Modified Caregiver Healthcare Task Difficulty and Preparedness Scale**	X	X	X	X
Nature and Intensity of Care	**Relationship to Patient**	X	X	X	X
	Hours of Care Provided	X	X	X	X
	Duration of Responsibility	X	X	X	X
	Nature of Assistance Provided	X	X	X	X
Healthcare Navigation Skills	**Liver Transplant Knowledge Questionnaire (LTKQ)**	X	X	X	X
Care Partner Burden	**Short Form Zarit Burden Interview (ZBI-12)**	X	X	X	X
Physical & General Health	**Physical & General Health Questionnaire**	X	X	X	X



Description of TEST Intervention

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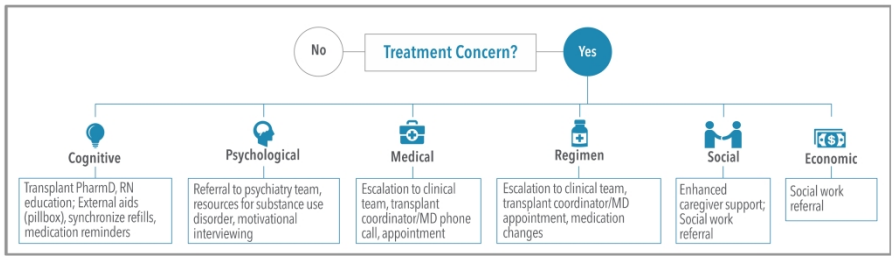

Categories of Two-Tiered Adherence Assessment

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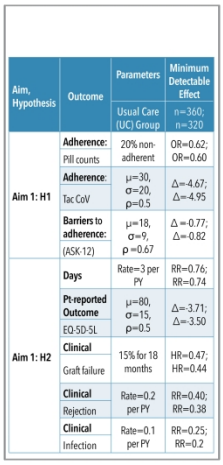

Aim, Hypothesis	Outcome	Parameters	Minimum Detectable Effect
		Usual Care (UC) Group	n=360; n=320
Aim 1: H1	Adherence: Pill counts	20% non-adherent	OR=0.62; OR=0.60
	Adherence: Tac CoV	μ=30, σ=20, ρ=0.5	Δ=-4.67; Δ=-4.95
	Barriers to adherence: (ASK-12)	μ=18, σ=9, ρ=0.67	Δ=-0.77; Δ=-0.82
Aim 1: H2	Days	Rate=3 per PY	RR=0.76; RR=0.74
	Pt-reported Outcome EQ-5D-5L	μ=80, σ=15, ρ=0.5	Δ=-3.71; Δ=-3.50
	Clinical Graft failure	15% for 18 months	HR=0.47; HR=0.44
	Clinical Rejection	Rate=0.2 per PY	RR=0.40; RR=0.38
	Clinical Infection	Rate=0.1 per PY	RR=0.25; RR=0.2

Power analyses

338x190mm (300 x 300 DPI)

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT AND HIPAA AUTHORIZATION FORM
Patient Consent Form

Protocol Title:	Technology Enabled Strategies to Promote Treatment Adherence in Liver Transplant: The TEST Trial
Principal Investigator:	Marina Serper, MD, MS Division of Gastroenterology and Hepatology 3400 Civic Center Boulevard, 7S PCAM 215-349-8222
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Sponsor	National Institute of Diabetes and Digestive and Kidney Diseases

Research Study Summary for Potential Subjects

You are being invited to participate in a research study. Your participation is voluntary, and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to understand different ways to improve medication adherence and health outcomes in individuals who have recently received a liver transplant.

If you agree to join the study, you will be asked to complete the following research procedures:

- Surveys about your current state of health
- Test of your cognitive functioning
- Functional health tests
- Questions about your medication regimen

Additionally, you may be randomly placed into a group of patients who receive enhanced post liver transplantation care. This includes but is not limited text message medication reminders, surveys asking about how you've been taking your medication, and appointment reminders. Your participation will last for 18 months (540 Days)

It is possible that patients who participate in this study may benefit in that they have a better understanding of their medication, how to take their medication, and how to recognize and report medication-related problems. This is a minimal risk study, but the most common risks of participation are feeling shame and/or some emotional discomfort when completing certain surveys or tests. Participation may also result in a loss of privacy.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. Your decision to participate in this research is voluntary, and you may choose to continue with your usual care routine from the transplant team. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?

You are being invited to participate in a research study because you are over the age of 18, have received a liver transplant in the past 3 months, and are English or Spanish-speaking.

Your doctor may be an investigator in this research study. You do not have to participate in any research study offered by your doctor. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. You may also decide to discuss the study with your family, friends, or family doctor. Being in a research study is different from being a patient. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study.

If you decide to participate, you will be asked to sign this form. You may be consented to this study through verbal consent, written consent, or eConsent. You will receive a copy of this consent form.

What is the purpose of this research study?

Liver transplantation is the only lifesaving treatment for end-stage liver disease. It has increasingly been performed on older adults who traditionally have more health issues. Medication adherence is key to making sure that patients who have undergone liver transplant do not develop more health issues. Taking medicine properly is important in making sure that a newly transplanted liver can function properly. However, adhering to post-transplant regimens is a very complex process with multiple medications and clinic

appointments. This study will see how readily available technology-enabled tools such as texting combined with transplant center resources and care partner support can optimize medication adherence, quality of life, and health outcomes among new liver transplant recipients.

How long will I be in the study?

If you choose to participate, you will be in this study for 18 months. The entire study including all participants will last a little over three years. There are two additional sites along with the University of Pennsylvania that will be enrolling participants. We anticipate to enroll 360 participants at all sites with 120 being enrolled at the University of Pennsylvania.

What am I being asked to do?

If you decide to participate, you will be randomized into one of two different groups. The first group will receive their normal standard of care from their transplant team with interviews at the beginning of the study, Month 6, Month 12, and Month 18. Interviews will last about 45-60 minutes and may include assessments that involve the following:

- Demographics
- Health status pre-transplant
- Details about your transplant surgery
- Montreal Cognitive Assessment (MoCA)
- Animal Naming Test (ANT)
- Rosenbaum Visual Acuity
- Liver Transplant Knowledge Questionnaire (LTKQ)
- Newest Vital Sign (NVS)
- 24-Hour Recall, Regimen Knowledge
- Tacrolimus Lab Values
- ASK-12
- EQ-5D-5L
- Alcohol, Tobacco, and Drugs Survey
- Grip Strength
- 30 Second Chair Stand
- Balance Test
- Liver Frailty Index Calculation
- Most Recent Height, Weight, and BP
- Laboratory Results

The second group is the intervention group. In addition to the interviews at the time points mentioned previously, participants in this group will also have interviews along with different text messages and alert reminders using our Way2Health (W2H) system:

- Monthly W2H adherence Assessment and Clinician Alerts
  - Patients and care partners will separately receive monthly, SMS text or online assessments of adherence barriers.
- Medication Reminders
  - Patient and care partners will receive twice-daily medication reminders
  - Patients and care partners will have the opportunity to change their text message preferences every 6 weeks and can opt out of reminders at any time.
- Laboratory and Appointment Notifications
  - Patients and care partners will receive transplant-specific reminders such as lab draws and clinic appointments
- Supplemental Self-Management Support
  - Patients and care partners will receive periodic supplemental information about their care through text messages and emails.

As a member of the TEST intervention group, you will have the option to turn on the above features for your care partner as well. Below is a table showing what will be asked of you or what you will be asked to do at each interview

Patient Study Measures and Outcomes		Interview Timepoint			
Variable	Instrument(s) or Measure(s)	BL (Day 0-90 +30)	6M (Day 180 +/- 30)	12M (Day 360 +/- 30)	18M (Day 540 +/- 30)
Informed Consent	Informed Consent	X			
Sociodemographics	Date of Birth	X			
	Age	X			
	Address	X			
	Sex Assigned at Birth	X			
	Gender Identity	X			
	Race	X			
	Ethnicity	X			
	Marital Status	X			
	Employment	X			
	Lifetime Occupational Complexity	X			
Pre and Peri-Operative Transplant Health Status	MELD score at time of LT	X			
	Liver Disease Etiology	X			
	Transplant Length of Stay	X			
	Discharge location	X			
	Medical Comorbidities	X			
Cognitive Status Measurement	Montreal Cognitive Assessment (MoCA)	X	X		X
	Animal Naming Test (ANT)	X	X		X
	Rosenbaum Visual Acuity	X	X		X
Social Support	Modified Support with Medication Management Scale	X	X	X	X
Healthcare Navigation Skills	Liver Transplant Knowledge Questionnaire (LTKQ)	X	X	X	X
Health Literacy	Newest Vital Sign (NVS)	X			
Medication Adherence	24-Hour Recall, Regimen Knowledge	X	X	X	X
	Tacrolimus Lab Values	X	X	X	X
	ASK-12	X	X	X	X
Health-Related Quality of Life	EQ-5D-5L	X	X	X	X
	Alcohol, Tobacco, and Drugs Survey	X	X	X	X
Functional Health Status	Grip Strength	X	X	X	X
	30 Second Chair Stand	X	X	X	X
	Balance Test	X	X	X	X
	Liver Frailty Index Calculation	X	X	X	X
	Most Recent Height, Weight, and BP	X	X	X	X
Chronic Disease Control	Lipids (LDL, TG) and eGFR	X	X	X	X
	HBA1C	X	X	X	X

A description of each measure is listed below:

- Sociodemographic Information- this is basic information that tells us a little bit more information about you. None of the information that we will be collecting in this portion of the study will be able to identify you.

- Pre and Peri-Operative Transplant Health Status- this information will help us understand a bit more about your history of liver disease and your transplant surgery.

- Cognitive Status Measurement- The Montreal Cognitive Assessment (MoCA) is an assessment to help detect mild cognitive impairment. It tests things such as memory, language, and attention. The Animal Naming Test (ANT) sees how

many animals you can name in a minute. The Rosenbaum Visual Acuity test is a measure of your eyesight.

- Measure of Social Support- The Medication Management Scale us used to understand your social support system by looking at how big it is as well as the kind of support you are receiving from friends and family.

- Healthcare Navigation Skills- The Liver Transplant Knowledge Questionnaire (LTKQ) is a measure of your knowledge and navigations skills in post-transplant scenarios.

- Health Literacy- Health literacy lets us know more about your knowledge when it comes to certain health topics. The Newest Vital Sign is a tool that is made up of questions asking you different health-related concepts such as how to read a nutrition label.

- Medication Adherence- Tacrolimus is one of the most common immunosuppressant drugs prescribed after liver transplant. We will check your tacrolimus lab values to see if they are where they should be. ASK-12 is a survey that also helps us measure medication adherence. It looks at certain topics like medication behavior, health beliefs, and forgetfulness. are used to see if you are taking the correct amount of your immunosuppression medication. Lastly, we will ask about your knowledge of the medications you've taken in the past 24 hours including but not limited to what they were prescribed for and the dose.

- Quality of Life- The EQ-5D-5L is used to assess your quality of life by looking at mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and self-rated health. The Tobacco, Alcohol, and Drugs survey asks you about your recent use of these items.

- Functional Health Status- Grip strength will be measured using a Jamar Dynamometer. The 30-Second Chair Stand test is a measure of leg strength and endurance. It involves seeing how many times you can stand up and sit back down in a chair. Lastly, the balance test will see how long you can hold a feet-together, semi-tandem and tandem stance. Measurements from these three tests will be used to calculate a score using the Liver Frailty Index (LFI). It is a measure testing your level of frailty by looking at your mobility, balance, and walking ability. Additionally, we will look at your most recent height, weight, and blood pressure measurements.

- Chronic Disease Control- At each interview, we will take note of your blood pressure, weight, eGFR (how well your kidneys are functioning), lipids (fats in your blood), and HBA1C (measure of how much sugar is in your blood).

An additional module of questions and educational videos may be assigned to you if you have a history of alcohol misuse or are at risk of alcohol misuse post-transplant.

The module consists of 12 education videos on topics related to recovery from substance misuse. Questionnaires will be sent out at varying time points to assess risk of relapse. Your participation in this module is not an optional component of the study if you are assigned to this group.

What are the possible risks or discomforts?

This is a minimal risk study. However, it is possible that subjects may feel shame and/or some emotional discomfort when taking some of the assessments. Feedback from these assessments will be provided to clinical staff.

There is also a small risk of loss of privacy since people outside of the study may look at records if necessary for oversight. However, you will only be identified by a study ID number, not by name or any other identifying information (e.g. personal and/or contact information). This will be kept separate from other data. All information will be kept in secure, password protected files.

Unless required by law, only the study team will have the authority to review any study records. In such cases, they too will be required to maintain confidentiality.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

If you are enrolled in the intervention study portion, you may directly benefit by having a better understanding of your medication, how to take your medication, and how to recognize and report any medication-related problems and other concerns to transplant center staff.

The results of the study may also provide important information regarding how strategies can be implemented to enhance safe medical adherence in transplant recipients. This may help other transplant centers start similar programs with their patients and caregivers.

What other choices do I have if I do not participate?

You do not have to participate in this study if you do not want to. Individuals that choose not to join the study will still receive their usual care.

Will I be paid for being in this study?

Participants (patients and care partners) will receive $30 for each interview they complete. With four interviews as part of the study at each time point, participants that complete it will receive $120 in total. You will be paid through ClinCard. It will require you to provide your social security number and fill out an I-9 form.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I have to pay for anything?

You do not have to pay for anything that is directly related to the study.

You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all interviews, and all information has been collected. We plan to end enrollment a little under 3 years after the beginning of the study and end the study a little under 4 years after starting. You will be expected to be a part of the study for a total of 18 months (1.5 years). This study may also be stopped at any time by the study investigator without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care. It will not impact your care or benefits. And data collected up to the point of your withdrawal will still be used as it will not include any identifying information. It will be documented whether or not each participant completes the study.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period. PHI in this study includes:

- Name
- Phone Number
- Email
- Date of Birth
- Age
- Address
- Zip Code
- Admission Date
- Date of Death
- Social Security Number

Each subject will be tracked using a Microsoft Excel database. The database, containing identifiers and other related information for coordinating research activities will be password protected and kept on the secure network drive at each site. Only the study team will have access this database.

Interview and Electronic Medical Record (EMR) data will be collected via REDCap. REDCap is a secure online data collection tool, which can only be accessed by authorized personnel listed on the project's IRB. Survey and text message (SMS) response data will be collected via W2H. W2H has a secure administrative platform that is password protected.

To reduce the risk of breach of confidentiality, a study identification number will be assigned to each subject in the study. This study ID will be the only means of communicating about the patient outside of the secure REDCap or Microsoft Access and will be the primary identifier in REDCap and Microsoft Access as well. All identifiable information will be deleted upon completion of the study (or as soon as a patient declines participation, if that is the case).

An external Data and Safety Monitoring Board (DSMB) will act in and advisory capacity to monitor participant's safety. They will evaluate study progress, review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. Should data be presented to the DSMB, it will be done so in a blinded manner. Participant identities will not be shared with the DSMB

Will information about this study be available to the public?

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you.

What may happen to my information collected on this study?

Future Use of Data

Your information will be de-identified. De-identified means that all identifiers have been removed. The information could be stored and shared for future research in this de-identified fashion. The information may be shared with other researchers within Penn or other research institutions. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

Electronic Medical Record and Release of Study Related Information

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of your medical chart within a health system. An EMR is simply a computerized version of a paper medical record.

If you have never received care within Penn Medicine and are participating in a University of Pennsylvania research study that uses Penn Medicine healthcare related services, an EMR will be created for you for the purpose of maintaining any information produced from your participation. The creation of this EMR is a requirement of your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). If you have been a patient at Penn Medicine in the past, information from your research participation will be added to your existing medical record.

What may be placed in the EMR?

Information related to your participation in the research (e.g., laboratory tests, notes from your physician, imaging studies, and clinical procedures, etc.) will be placed in your EMR maintained by Penn Medicine.

Once placed in your EMR your information may be accessible to appropriate Penn Medicine workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by Penn Medicine to be appropriate to have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

Penn Medicine also participates in automated information sharing through Health Information Exchanges (HIEs). HIEs securely share parts of your electronic health record, including research information, with other healthcare organizations involved in your care. This information is shared to improve the quality, safety and efficiency of your

healthcare. To request that your health information not be shared through HIEs, please call 215-662-4484.

Will I, as a subject, have access to research related information within the EMR/?

The 21st Century Cures Act requires healthcare institutions to allow patients increased access to their electronic medical record. As part of your participation in this research, you will have access to research related information within your EMR through Penn Medicine's patient portal – called MyPennMedicine (MPM).

Some information specific to this clinical research study may be shared with you in a delayed manner, shared with you at the end of the study, or not shared with you. Not sharing or delaying certain research information within your EMR may be necessary to protect the integrity of the trial results or for other reasons.

No information form this study will be kept in your EMR. Any results from interviews or assessments will not be stored in your EMR. However, communication about the study will be sent through EMR system to clinicians as needed. This will not be viewable in MPM.

Will I receive the results of research testing that may be relevant to my health?

Many of tests done in research studies are only for research and have no clear impact on your healthcare. Research results for this study will not be returned to you because they would not be relevant to your healthcare.

However, you may check the study at ClinicalTrials.gov to see any study information that may be published.

What information about me may be collected, used or shared with others?

The following identifying information will be collected from you for purposes of communicating with you about the study and tracking your study progress:

- Name
- Phone number
- Email

This information will be kept in a secure, password-protected excel database. It will not be used for purposes of research nor shared with other individuals or entities outside of the study team at Penn.

We will gather the below identifying information for purposes of conducting the research. It will not be shared with individuals outside of the study team at the study sites:

- Date of Birth
- Age
- Address

- Zip Code
- Admission Date
- Date of Death

This information will be input into the password-protected and encrypted database REDCap.

Non-identifying information that will be collected from you will include:

- Demographic information (e.g. sex, race/ethnicity, etc.)
- Information about your liver transplant
- Information about your health history
- Results of any assessments performed (e.g. MoCA, Newest Vital Sign, etc.)
- Clinical outcomes (e.g. days hospitalized, transplant complicates, etc.)
- Medical information in regards to your health status throughout the study (e.g. blood pressure, weight, eGFR)

This information will also be input into the password-protected and encrypted database REDCap. This information will be shared with other study sites.

Lastly, we will need to collect your Social Security Number in order to provide you payment for your participation in this study. This information will not be stored electronically. We will ask this information from you in-person or over the phone and write it down on the appropriate forms. These forms will then be stored in a locked cabinet for security.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Where may my information be stored?

Each subject will be tracked using a Microsoft Excel database. The database, containing identifiers and other related information for coordinating research activities will be password protected and kept on the secure network drive at each site. Only the study team will have access this database.

Interview and Electronic Medical Record (EMR) data will be collected via REDCap. REDCap is a secure online data collection tool, which can only be accessed by authorized personnel listed on the project's IRB. Survey and text message (SMS) response data will be collected via W2H. W2H has a secure administrative platform that is password protected.

To reduce the risk of breach of confidentiality, a study identification number will be assigned to each subject in the study. This study ID will be the only means of communicating about the patient outside of the secure REDCap or Microsoft Access and will be the primary identifier in REDCap and Microsoft Access as well. All identifiable information will be deleted upon completion of the study (or as soon as a patient declines participation, if that is the case).

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn Medicine and the University of Pennsylvania, including offices that support research operations
- Authorized study personnel at Northwest University and the University of Miami
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of Penn Medicine, might receive my information?

Outside organizations

- Individuals on the DSMB will be able to received blinded, de-identified information about you.
- Authorized study members at Northwestern University and the University of Miami will have access to de-identified information
- The study sponsor, National Institute on Aging (NIA)

Oversight organizations

- The U. S. Office of Human Research Protections (OHRP)
- National Institute of Health (NIH)

Once your personal health information is disclosed to others outside Penn Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to Penn Medicine procedures developed to protect your privacy.

How long may Penn Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

However, Penn Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission

- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document, you are permitting Penn Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the number on page one of this form.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	
Name of Subject (Please Print)	Signature of Subject	Date
_____	_____	
Name of Person Obtaining	Signature	Date

Consent (Please Print)

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Care Partner Consent Form

Protocol Title:	Technology Enabled Strategies to Promote Treatment Adherence in Liver Transplant: The TEST Trial
Principal Investigator:	Marina Serper, MD, MS Division of Gastroenterology and Hepatology 3400 Civic Center Boulevard, 7S PCAM 215-349-8222
Emergency Contact:	Alex Burdzy Division of Gastroenterology and Hepatology 3400 Civic Center Boulevard, 7S PCAM 215-662-3904
Sponsor	National Institute of Diabetes and Digestive and Kidney Diseases

Research Study Summary for Potential Subjects

You are being invited to participate in a research study. Your participation is voluntary, and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to understand different ways to improve medication adherence and health outcomes in individuals who have recently received a liver transplant.

If you agree to join the study, you will be asked to complete the following research procedures:

- Interviews about your role in the patient's care
- Surveys about your caregiving ability

Additionally, you may be randomly placed into a group of patients and care partners who are part of enhanced post liver transplantation care. This includes but is not limited text message medication reminders for the patient, surveys asking about how the

patient has been taking their medication, and appointment reminders. Your participation will last for 18 months (540 Days).

It is possible that care partners who participate in this study may benefit in that they have a better understanding of transplant medication and how to recognize and report medication-related problems. This is a minimal risk study, but the most common risks of participation are feeling shame and/or some emotional discomfort when completing certain surveys or tests. Participation may also result in a loss of privacy.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. Your decision to participate in this research is voluntary, and you may choose to continue with your usual care routine from the transplant team. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?

You are 18 years or older, are English or Spanish speaking, and provide care for a recent transplant recipient.

The patient's doctor may be an investigator in this research study. You do not have to participate in any research study offered by this doctor. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. You may also decide to discuss the study with your family, friends, or family doctor. Being in a research study is different from being a patient. As an investigator, the patient's doctor is interested both in their clinical welfare and in the conduct of this study.

If you decide to participate, you will be asked to sign this form. You may be consented to this study through verbal consent, written consent, or eConsent. You will receive a copy of this consent form.

What is the purpose of this research study?

Liver transplantation is the only lifesaving treatment for end-stage liver disease. It has increasingly been performed on older adults who traditionally have more health issues. Medication adherence is key to making sure that patients who have undergone liver transplant do not develop more health issues. Taking medicine properly is important in making sure that a newly transplanted liver can function properly. However, adhering to post-transplant regimens is a very complex process with multiple medications and clinic appointments. This study will see how readily available technology-enabled tools such as texting combined with transplant center resources and care partner support can optimize medication adherence, quality of life, and health outcomes among new liver transplant recipients.

How long will I be in the study?

If you choose to participate, you will be in this study for 18 months. The entire study including all participants will last a little over three years. There are two additional sites along with the University of Pennsylvania that will be enrolling participants. We anticipate to enroll 360 participants at all sites with 120 being enrolled at the University of Pennsylvania.

What am I being asked to do?

The patient you care for will be randomly assigned to one of two groups. The first group will receive their normal standard of care from their transplant team with interviews at the beginning of the study, Month 6, Month 12, and Month 18. Interviews will last about 45-60 minutes and may include assessments that involve the following:

- Demographics
- Caregiver Inventory (CGI)
- Modified Caregiver Healthcare Task Difficulty and Preparedness Scale
- Relationship to the patient
- Hours of care provided
- Duration of responsibility
- Nature of assistance provided
- Liver Transplant Knowledge Questionnaire (LTKQ)
- Short Form Zarit Burden Interview (ZBI-12)

The second group is the intervention group. In addition to the interviews at the time points mentioned previously, participants in this group will also have interviews along with different text messages and alert reminders using our Way2Health (W2H) system:

- Monthly W2H adherence Assessment and Clinician Alerts
  - Patients and care partners will separately receive monthly, SMS text or online assessments of adherence barriers.
- Medication Reminders
  - Patient and care partners will receive twice-daily medication reminders
  - Patients and care partners will have the opportunity to change their text message preferences every 6 weeks and can opt out of reminders at any time.
- Laboratory and Appointment Notifications
  - Patients and care partners will receive transplant-specific reminders such as lab draws and clinic appointments
- Supplemental Self-Management Support
  - Patients and care partners will receive periodic supplemental information about their care through text messages and emails.

You will not be assigned to one of these groups. However, if the patient you care for is assigned to the intervention group, you may also receive text messages and alerts from the W2H system.

Below is a table showing what will be asked of you or what you will be asked to do at each interview

Care Partner Study Measures and Outcomes		Interview Timepoint			
Variable	Instrument(s) or Measure(s)	BL (Day 0-90 +30)	6M (Day 180 +/- 30)	12M (Day 360 +/- 30)	18M (Day 540 +/- 30)
Informed Consent	Informed Consent	X			
Sociodemographics	Date of Birth	X			
	Age	X			
	Address	X			
	Sex Assigned at Birth	X			
	Gender Identity	X			
	Race	X			
	Ethnicity	X			
	Marital Status	X			
	Employment	X			
	Lifetime Occupational Complexity	X			
Self-Efficacy	Caregiver Inventory (CGI)	X	X	X	X
Preparedness	Modified Caregiver Healthcare Task Difficulty and Preparedness Scale	X	X	X	X
Nature and Intensity of Care	Relationship to Patient	X	X	X	X
	Hours of Care Provided	X	X	X	X
	Duration of Responsibility	X	X	X	X
	Nature of Assistance Provided	X	X	X	X
Healthcare Navigation Skills	Liver Transplant Knowledge Questionnaire (LTKQ)	X	X	X	X
Care Partner Burden	Short Form Zarit Burden Interview (ZBI-12)	X	X	X	X

A description of each measure is listed below:

- Sociodemographic Information- this is basic information that tells us a little bit more information about you. None of the information that we will be collecting in this portion of the study will be able to identify you.

- Self-Efficacy- The Caregiver Inventory looks at a care partner's own self-care and possible positive aspects of caregiving.

- Preparedness- The Modified Caregiver Healthcare Task Difficulty and Preparedness Scale is a survey seeing if the care partner assists the transplant recipient with different tasks, and if so, how much difficulty they have performing the task. We will evaluate if tasks are scored as no difficulty, low, medium, or high difficulty.

- Nature and Intensity of Care Provided- This includes asking you about your relationship to the liver transplant recipient, hours of care you provide throughout the week, how long you have been a care partner, and how long it takes to travel to get to the transplant recipient's place of residence.

- Healthcare Navigation Skills- The Liver Transplant Knowledge Questionnaire (LTKQ) is a measure of your knowledge and navigations skills in post-transplant scenarios.

- Care Partner Burden- The Short Form Zarit Burden Interview (ZBI-12) measures the degree of burden related to the demands of daily care provided to a dependent. It is used to evaluate the influence exerted on a care partner's physical and psychological health.

What are the possible risks or discomforts?

This is a minimal risk study. However, it is possible that subjects may feel shame and/or some emotional discomfort when taking some of the assessments. Feedback from these assessments will be provided to clinical staff.

There is also a small risk of loss of privacy since people outside of the study may look at records if necessary for oversight. However, you will only be identified by a study ID number, not by name or any other identifying information (e.g. personal and/or contact information). This will be kept separate from other data. All information will be kept in secure, password protected files.

Unless required by law, only the study team will have the authority to review any study records. In such cases, they too will be required to maintain confidentiality.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

If you are enrolled in the intervention study portion, the patient may directly benefit by having a better understanding of their medication, how to take their medication, and how to recognize and report any medication-related problems and other concerns to transplant center staff.

The results of the study may also provide important information regarding how strategies can be implemented to enhance safe medical adherence in transplant recipients. This may help other transplant centers start similar programs with their patients and care partners.

What other choices do I have if I do not participate?

You do not have to participate in this study if you do not want to. Individuals that choose not to join the study will still receive their usual care.

Will I be paid for being in this study?

Participants (patients and care partners) will receive $30 for each interview they complete. With four interviews as part of the study at each timepoint, participants that complete it will receive $120 in total. You will be paid through ClinCard. It will require you to provide your social security number and fill out an I-9 form.

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You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all interviews, and all information has been collected. We plan to end enrollment a little under 3 years after the beginning of the study and end the study a little under 4 years after starting. You will be expected to be a part of the study for a total of 18 months (1.5 years). This study may also be stopped at any time by the study investigator without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care. It will not impact your care or benefits. And data collected up to the point of your withdrawal will still be used as it will not include any identifying information. It will be documented whether or not each participant completes the study.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period. PHI in this study includes:

- Name
- Phone Number
- Email
- Date of Birth
- Age
- Address
- Zip Code
- Social Security Number

Each subject will be tracked using a Microsoft Excel database. The database, containing identifiers and other related information for coordinating research activities will be password protected and kept on the secure network drive at each site. Only the study team will have access this database.

Interview and Electronic Medical Record (EMR) data will be collected via REDCap. REDCap is a secure online data collection tool, which can only be accessed by authorized personnel listed on the project's IRB. Survey and text message (SMS) response data will be collected via W2H. W2H has a secure administrative platform that is password protected.

To reduce the risk of breach of confidentiality, a study identification number will be assigned to each subject in the study. This study ID will be the only means of communicating about the patient outside of the secure REDCap or Microsoft Access and will be the primary identifier in REDCap and Microsoft Access as well. All identifiable information will be deleted upon completion of the study (or as soon as a patient declines participation, if that is the case).

An external Data and Safety Monitoring Board (DSMB) will act in and advisory capacity to monitor participant's safety. They will evaluate study progress, review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. Should data be presented to the DSMB, it will be done so in a blinded manner. Participant identities will not be shared with the DSMB

Will information about this study be available to the public?

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you.

What may happen to my information collected on this study?

Future Use of Data

Your information will be de-identified. De-identified means that all identifiers have been removed. The information could be stored and shared for future research in this de-identified fashion. The information may be shared with other researchers within Penn or other research institutions. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

Electronic Medical Record and Release of Study Related Information

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of your medical chart within a health system. An EMR is simply a computerized version of a paper medical record.

If the patient has never received care within Penn Medicine and is participating in a University of Pennsylvania research study that uses Penn Medicine healthcare related services, an EMR will be created for them for the purpose of maintaining any information produced from your participation. The creation of this EMR is a requirement of their participation in this study. In order to create their EMR, the study team will need to obtain basic information about them that would be similar to the information they would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). If they have been a patient at Penn Medicine in the past, information from your research participation will be added to your existing medical record.

As a care partner, we will not be created an EMR for you at Penn.

What may be placed in the EMR?

Information related to your participation in the research (e.g., laboratory tests, notes from your physician, imaging studies, and clinical procedures, etc.) will be placed in your EMR maintained by Penn Medicine.

Once placed in the EMR, the patient's information may be accessible to appropriate Penn Medicine workforce members that are not part of the research team. Information within the EMR may also be shared with others who are determined by Penn Medicine to be appropriate to have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

Penn Medicine also participates in automated information sharing through Health Information Exchanges (HIEs). HIEs securely share parts of your electronic health record, including research information, with other healthcare organizations involved in

your care. This information is shared to improve the quality, safety and efficiency of your healthcare. To request that your health information not be shared through HIEs, please call 215-662-4484.

Will I, as a subject, have access to research related information within the EMR/?
The 21st Century Cures Act requires healthcare institutions to allow patients increased access to their electronic medical record. As part of the patient's participation in this research, they will have access to research related information within their EMR through Penn Medicine's patient portal – called MyPennMedicine (MPM).

Some information specific to this clinical research study may be shared with them in a delayed manner, shared with them at the end of the study, or not shared with them. Not sharing or delaying certain research information within their EMR may be necessary to protect the integrity of the trial results or for other reasons.

No information from this study will be kept in their EMR. Any results from interviews or assessments will not be stored in their EMR. However, communication about the study will be sent through EMR system to clinicians as needed. This will not be viewable in MPM.

Will I receive the results of research testing that may be relevant to my health?

Many of tests done in research studies are only for research and have no clear impact on your healthcare. Research results for this study will not be returned to you because they would not be relevant to your healthcare.

However, you may check the study at ClinicalTrials.gov to see any study information that may be published.

What information about me may be collected, used or shared with others?

The following identifying information will be collected from you for purposes of communicating with you about the study and tracking your study progress:

- Name
- Phone number
- Email

This information will be kept in a secure, password-protected excel database. It will not be used for purposes of research nor shared with other individuals or entities outside of the study team at Penn.

We will gather the below identifying information for purposes of conducting the research. It will not be shared with individuals outside of the study team at the study sites:

- Date of Birth
- Age

- Address
- Zip Code

This information will be input into the password-protected and encrypted database REDCap.

Non-identifying information that will be collected from you will include:

- Demographic information (e.g. sex, race/ethnicity, etc.)
- Information about your liver transplant
- Information about your health history
- Results of any assessments performed (e.g. MoCA, Newest Vital Sign, etc.)
- Clinical outcomes (e.g. days hospitalized, transplant complicates, etc.)
- Medical information in regards to your health status throughout the study (e.g. blood pressure, weight, eGFR)

This information will also be input into the password-protected and encrypted database REDCap. This information will be shared with other study sites.

Lastly, we will need to collect your Social Security Number in order to provide you payment for your participation in this study. This information will not be stored electronically. We will ask this information from you in-person or over the phone and write it down on the appropriate forms. These forms will then be stored in a locked cabinet for security.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Where may my information be stored?

Each subject will be tracked using a Microsoft Excel database. The database, containing identifiers and other related information for coordinating research activities will be password protected and kept on the secure network drive at each site. Only the study team will have access this database.

Interview and Electronic Medical Record (EMR) data will be collected via REDCap. REDCap is a secure online data collection tool, which can only be accessed by authorized personnel listed on the project's IRB. Survey and text message (SMS) response data will be collected via W2H. W2H has a secure administrative platform that is password protected.

To reduce the risk of breach of confidentiality, a study identification number will be assigned to each subject in the study. This study ID will be the only means of

communicating about the patient outside of the secure REDCap or Microsoft Access and will be the primary identifier in REDCap and Microsoft Access as well. All identifiable information will be deleted upon completion of the study (or as soon as a patient declines participation, if that is the case).

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn Medicine and the University of Pennsylvania, including offices that support research operations
- Authorized study personnel at Northwest University and the University of Miami
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of Penn Medicine, might receive my information?

Outside organizations

- Individuals on the DSMB will be able to received blinded, de-identified information about you.
- Authorized study members at Northwestern University and the University of Miami will have access to de-identified information
- The study sponsor, National Institute on Aging (NIA)

Oversight organizations

- The U. S. Office of Human Research Protections (OHRP)
- National Institute of Health (NIH)

Once your personal health information is disclosed to others outside Penn Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to Penn Medicine procedures developed to protect your privacy.

How long may Penn Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

However, Penn Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document, you are permitting Penn Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the number on page one of this form.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	
Name of Subject (Please Print)	Signature of Subject	Date
_____	_____	
Name of Person Obtaining Consent (Please Print)	Signature	Date

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2, 14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	6

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-9
Objectives	#7	Specific objectives or hypotheses	7-8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	3-5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14, 15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5-6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	5

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-6

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8-9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	9

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5-6
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	1, 14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A