Patient randomised 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 centres 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-randomised prospective clinical trial at three transplant centres in the Northeast, Midwest and South to investigate the effects of a remotely administered adherence programme compared with usual care. The programme monitors potential non-adherence largely leveraging 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 (eg, days hospitalised). 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 the TEST trial. Results will be published in peer-reviewed journals and summaries will be provided to study funders.

Trial registration number NCT05260268.

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, LT recipients (LTRs) manage complex IS 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 all requiring robust health literacy and self-management skills. LTRs take on average 11 medications and 39% report a medication change within the past 30days.6 Additionally, 38% of LT candidates have inadequate health literacy,7 and lower health literacy is associated with poor treatment knowledge and higher IS non-adherence.8–9 Post-transplant non-adherence ranges from 17% to 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 one of five LTRs.16 Up to 25% of late acute rejection episodes (>6 months post-LT and likely due to behavioural factors) are suspected to be caused by poor adherence.17–18

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ This is a multi-centre 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.
Compounding this issue is the fact that often more intensive medical management is needed post-LT as IS leads to worsening hypertension, diabetes and excessive weight gain. 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. 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). Guided by our conceptual framework, we leverage widely available technology (electronic health record (EHR), mobile devices) in a ‘low touch’ manner to support and track regimen use and activate appropriate transplant centre clinical staff when specific problems are identified. Here, we provide overview of the TEST strategy and describe the methods and rationale for evaluating this approach in a randomised-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 two-arm, prospective, patient-randomised, controlled trial at three large, diverse transplant centres 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 with 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 centre factors associated with optimal implementation; (3) assess the cost-effectiveness of TEST from a transplant centre 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 2022 to April 2027. The Penn Transplant Clinic (UPenn) is the largest multi-organ transplant centre in the Mid-Atlantic and ranks in the top 10 centres nationally with about 130–140 LTs annually. Northwestern Medicine Kovler Organ Transplant Center (Northwestern) is a large transplant centre 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 centres in the US 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 three 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 behavioural toolkit—Way to Health (W2H). Patients randomised 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 centre staff between clinic visits and (3) tailored clinical support based on individual challenges. The below components make up the TEST strategy:

- **Two-tiered adherence assessments and 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 non-adherence (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 EHR; at Miami and Northwestern clinical research coordinators (RCs) will escalate the potential non-adherence alerts to the clinical team via email.

- **Medication reminders:** at enrolment, we will send the patient and designated care partner two times a day 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 customise the timing of these messages (two times a day, daily or opt out).

- **Laboratory and appointment notifications:** the W2H portal will send pre-programmed text message laboratory and appointment reminders starting within 3 months of enrolment 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 centres as part of usual care and that additional messages from the study may be burdensome.

- **Supplemental self-management support:** to maintain long-term health, LTRs must engage in routine appointments with primary or specialty care, receive follow-up imaging (eg, 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 Programme (RSP) will be available for LTRs with moderate to high-risk pretransplant alcohol use disorder, 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 enrol 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-speaking or Spanish-speaking; (4) home-dwelling; (5) owns a smartphone and is comfortable receiving text messages and/or accessing the internet via smartphone. Care partner eligibility includes: (1) 18 years or older; (2) English-speaking or Spanish-speaking; (3) has access to a smartphone and is comfortable receiving text messages and/or accessing the internet via smartphone. Patients and/or care partners will be excluded if they have severe uncorrectable vision, hearing or cognitive impairments that may impede study interviews.

**Randomisation and blinding**

Block randomisation 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 randomised via the W2H platform at the beginning of the baseline visit. Patients randomised 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 RCs, 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. RCs will obtain signed informed consent from all participants prior to their enrolment in the trial (see attached in online supplemental material).

**Recruitment and data collection**

Recruitment will begin with RCs prescreening potentially eligible patients in the 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 enrol 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, 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. Preoperative and perioperative transplant health status will be measured by the Model for End-Stage Liver Disease (MELD) score at the time of LT, liver disease aetiology, transplant hospitalisation length of stay, discharge location and medical comorbidities. Cognitive function will be measured with the Montreal Cognitive Assessment, the Animal Naming Test and visual acuity using the Rosenbaum Pocket Vision Screening Card using PV Numbers. We will use the Support with Medication Management Scale which assesses social support. 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 IS timing and side effects. We will assess health literacy with the Newest Vital Sign.

**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. Preparedness of the care partner will be measured through the Caregiver Healthcare Task Difficulty and Preparedness Scales. 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).

**Outcomes**

**Medication adherence**

The primary adherence outcome 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. Additional secondary adherence measures include (2) the ASK-12 scale that assesses general medication attitudes and beliefs, (3) regimen knowledge and (4) a biological measure using tacrolimus intrapatient 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 three adherence related-sub scales: medication behaviour, health beliefs and inconvenience/forgetfulness. 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 IS variability will be assessed with the tacrolimus coefficient of variation (CoV) (100xSD/mean tacrolimus concentration), the medication level variability index (MLVI, SD of at least three values), and tacrolimus time in the therapeutic
Table 1  Study measures and timing of assessments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Instrument(s) or measure(s)</th>
<th>Interview timepoint</th>
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<td>HbA1c</td>
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Care partner study measures and outcomes

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range (TTR).\textsuperscript{56–58} Tacrolimus variability is associated with non-adherence (eg, wrong or skipped dose, wrong drug timing, wrong laboratory timing), medication toxicity, kidney injury and poorer survival.\textsuperscript{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 five questions, each with five possible answers, and, separately, self-rated health on a vertical visual analogue scale.\textsuperscript{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 LFI that combines grip strength, balance and timed chair stand measures to classify patients’ frailty severity.\textsuperscript{63}

Clinical outcomes
We will assess (1) days hospitalised, (2) days alive and out of hospital (DAOH), (3) liver graft outcomes: liver graft rejection and liver graft failure, (4) mortality. Days hospitalised and DAOH are both patient-centred, clinical outcomes validated for clinical trials.\textsuperscript{30 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.\textsuperscript{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) haemoglobin A1c (HbA1c), (3) lipid profile (low-density lipoprotein cholesterol (LDL), triglycerides (TG)) and (4) kidney function measured by estimated rate (estimated glomerular filtration rate (eGFR); mL/min/1.73m²).

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.\textsuperscript{20 51}

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

Costs
The cost of the TEST strategy will be conducted at UPenn LT and will be analysed 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 centre 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, 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: (1) 24-hour recall, (2) ASK-12, (3) regimen knowledge and (4) 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 four time-interval specific Tac-CoV values modelled 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 modelled as a continuous outcome using the same approach. We will also carry out sensitivity analyses to further evaluate models: (1) we will repeat the analysis using different percentage thresholds to define pill count adherence (eg, 90%) and will also evaluate adherence as a continuous measure. We will replace Tac-CoV with the MLVI (computed as tacrolimus SD) and will analyse the MLVI as a continuous and as a binary outcome (MLVI>2).

We will analyse tacrolimus TTR as an additional outcome. Secondary outcomes of interest for aim 1 include: (1) better health status and fewer hospitalisation days as well as (2) more optimal chronic disease control. Better health status and fewer hospitalisation days will be measured through (i) days hospitalised, (ii) HRQoL, (iii) graft failure, (iv) graft rejection and (v) infections. Days hospitalised will be modelled 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 modelled 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 dropout exceeds 10%, we will use inverse probability of censoring weighting, such that the weighted complete data represent the study sample. Multiple imputation, 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, V.9.4).

For aim 2, we will determine the fidelity of each component of the intervention over time and investigate patient, care partner, provider or transplant centre factors associated with optimal implementation. Mixed methods will be employed using a convergent parallel design to obtain data on intervention implementation. We will capture four 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-month 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 (eg, 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 modelled 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 (ie, intervention vs usual care) and fidelity through interaction terms. For each time point (eg, 12 months), we will have a covariate for survey completion fraction during the preceding follow-up interval (eg, 5/6 surveys completed for months 7–12).

For aim 3, we will assess the costs and cost-effectiveness of the TEST intervention from a transplant centre perspective. We will evaluate the cost-effectiveness of the TEST intervention, relating implementation costs to any changes in HRQoL, as measured by the EQ-5D-5L. We will also relate implementation costs to medication adherence and days hospitalised, the primary and secondary trial outcomes. The costing and cost-effectiveness analyses will be summarised in the form of centre costs per LTR (with detail by type of cost) and in incremental cost-effectiveness ratios that show the difference in implementation costs between intervention and control arms divided by the difference in health outcome (eg, 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 on request.

ETHICS AND DISSEMINATION
The University of Pennsylvania Review Board has approved the study as the 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 three 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 include a statement acknowledging the posting of eligibility criteria and study information on clinicaltrials.gov, as well as the subsequent results.

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Patient and public involvement Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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