PROTOCOL TITLE: Transplant Regimen Adherence for Kidney Recipients by Engaging Information Technologies: The TAKE IT Trial

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1.0 Objectives:

1.1 Specific Aims and hypotheses are to:

Aim 1: Test the effectiveness of the TAKE IT strategy, compared to usual care, to improve kidney transplant (KT) recipients':

H_1: treatment knowledge (indications, potential side effects, demonstrated proper use)

H_2: medication use (regimen adherence via self-report, pill count, tacrolimus levels)

H_3: transplant-specific outcomes (Δ eGFR, quality of life, re-hospitalization)

H_4: chronic disease outcomes (blood pressure, HbA1c)

Aim 2: Examine the persistence of any effects of the TAKE IT strategy on outcomes over 2 years among new and established KT recipients.

Aim 3: Evaluate the fidelity of each component of the TAKE IT strategy over time, and investigate any patient, provider, or transplant center barriers to implementation.

Aim 4: Determine the costs of delivering the TAKE IT strategy from a transplant center perspective.

2.0 Background:

2.1 Kidney Transplantation Benefits Individuals with End-Stage Renal Disease.

Over 26 million adults suffer from chronic kidney disease, and >400,000 have end-stage renal disease (ESRD) leaving them dialysis-dependent.[1-3] For many ESRD patients, kidney transplantation (KT) is the optimal treatment as it provides longer survival, better quality of life, less morbidity, and lower hospitalization rates compared to dialysis.[2, 4, 5] It also is more cost-effective within 2 years of KT compared to dialysis (~$88,000/year).[3]

2.2 KT Recipients Must Manage Complex Prescription Drug Regimens.

In 2015, 17,000+ individuals received a KT either from a deceased or living donor. Despite the advantages, a third of KTs fail within 5 years- mostly due to host rejection of the organ (graft).[6, 7] To prevent this, KT recipients must adhere to immunosuppressive (IS) medication regimens that require constant monitoring of therapeutic levels. Failure to do so may result in life-threatening, costly complications. For example, under-immunosuppression (levels too low) may lead to graft rejection, but over-immunosuppression (levels too high) increases risks of opportunistic infections and malignancies.[8] IS-related complications can require costly treatments and hospitalizations. The most common IS medications are calcineurin inhibitors (CNIs). While effective, they have many side effects (electrolyte derangements, neurological complications, weight gain, kidney injury, hypertension, diabetes, cognitive/mood changes).[9-11] CNIs may interact with other drugs, causing life-threatening complications.[11, 12]

From a patient perspective, the narrow therapeutic range of IS medications requires constant monitoring via multi-weekly or monthly blood draws to achieve 'target' drug levels, which leads to frequent dose adjustment. Patients are informed of these medication changes often by phone and without written instructions; this increases the risk of confusion as existing regimen information and R_x labels become outdated. Patients must also precisely time their dosing of IS medications with blood draws for drug levels to be accurate. Otherwise, dose adjustments may be incorrect and cause further harm. In addition to transplant medications, patients are taking other regimens for comorbid conditions often prescribed by multiple healthcare providers.[11, 13] According to recent pilot data from Northwestern, KT recipients take on average 11 R_x medications.

2.3 Poor Medication Adherence is Common among KT Recipients.

Problems with medication adherence have long been linked to a variety of negative outcomes in a range of chronic disease states. Half of patients living with diabetes or a cardiovascular condition take less than 80% of their prescribed doses.[14-17] Adherence-related problems are estimated to cost the US healthcare system up to $300 billion a year, compromising the effectiveness and safety of a patient's treatment, leading to >125,000 deaths per year.[16]

Data specific to transplantation is becoming more robust. Recent meta-analyses identified the prevalence of 'poor' adherence (<80% of prescribed doses taken) to IS medications to be high (~35%) among KT recipients.[13, 18-20] The consequences are also clear; Nevins et al. found that declining medication adherence immediately after KT significantly increased risk and frequency of acute rejection.[21] Factors associated with poor adherence were minority ethnicity, poorer self-reported health, and less social support, although few studies examined these or other factors such as health literacy.[18, 22] While existing research on medication adherence in KT is limited by methodological weaknesses (unequal length of follow up, small sample size, retrospective study design, variability in definition of non-adherence), problems that have been identified mirror those patients face in other chronic diseases. Given the complexity of changing regimens, these challenges may be equal or greater in KT.[13, 23]

Numerous studies have shown that socioeconomically disadvantaged patients, the elderly, racial/ethnic minorities, those with less education and limited health literacy are more likely to experience medication-related problems.[24-28] In fact, evidence suggests that inadequate medication adherence may be a root cause of many of the negative health outcomes experienced by these vulnerable groups.[29, 30] As KT recipients are typically older, issues of inadequate health literacy are further compounded by cognitive decline either due to age or effects of IS medications. But greater involvement of the patient in healthcare and decision-making places greater demands on their health literacy and numeracy skills.[31] Patients with low health literacy are less able to adequately communicate with healthcare providers.[32] A third of patients with chronic kidney disease have low health literacy.[33] In this population, low health literacy is associated with minority race, low SES, older age, and reduced referral for transplantation.[32-34] According to the Agency for Healthcare Research and Quality (AHRQ), poor health outcomes are due in part to differences in patient-provider communication, and poor health literacy.[35] A 2016 study by Covert et al.

examined post-transplant processes in care. Patients' inadequate understanding of medications was the strongest predictor of non-adherence and 30-day readmissions.[20]

2.4 Preliminary Data: Prevalence of Transplant Adherence and Barriers.

We recently conducted interviews with 99 KT recipients at Northwestern and Emory Universities. 24% of participants had limited literacy. Patients were taking an average of 11 (SD=4) medications; one third (32%) had a medication change in the past month. 1 in 4 KT recipients could not demonstrate proper regimen use for IS regimens and 35% were poorly adherent based on self-report or by tacrolimus level standard deviation. In multivariable analyses, fewer months since transplant and limited literacy were associated with poor adherence (all $p<0.05$). In multivariable models, patients over 65 (OR 2.45, 95%CI 1.20-4.98), non-white race (OR 2.83, 95% CI 1.54-5.20), demonstrating improper regimen use (OR 1.15, 95% CI 1.01-1.30) and inadequate adherence (OR 2.10, 95%CI 1.10-4.01) had a higher post-transplant hospitalization risk.[36, 37]

2.5 Evidence of Medication Adherence Interventions in KT is Limited.

Few interventions to improve medical adherence have been tested among KT recipients. In 2 recent systematic reviews examining behavioral/self-management interventions, one broadly in solid organ transplant and the other specific to KT recipients (only 12 studies per review), very few had a randomized controlled trial design and/or were rated methodologically strong by reviewers.[38-41] Interventions utilized various strategies such as enhanced education sessions, clinical pharmacist services, and electronic monitoring and feedback with mixed results. Low and colleagues highlighted that interventions that including support tools to help patients remember to take their medicine, as well as monitoring strategies were most effective. Both reviews concluded that evidence of effective strategies to promote medication adherence were considerably limited.[38, 39]

2.6 Conceptual Framework: Deconstructing and Simplifying Medication Use.

Patients must take several steps to manage multi-drug regimens; each has unique challenges impacting adherence.[42] The first is to fill their prescriptions. Failure to fill or refill prescriptions is common.[43, 44] The ability to name, identify and understand how to take medications in one's Rx regimen is also fundamental, yet often an overlooked, part of adherence. This is increasingly difficult as patients' drugs are frequently changed by prescribers and/or switched for generic versions by insurers.[45, 46] Additionally, patients taking complex regimens may confuse one drug for another.[47] Studies conducted by members of this team found 75% of patients cannot accurately identify their Rx regimen, and almost half (46%) misinterpret dose or timing of a prescription.[48, 49] These problems have been linked to chronic disease outcomes.[48] Studies have also repeatedly shown that many patients do not organize multi-drug regimens in the most efficient manner to sustain adherence.[50-53] Next, a fundamental part of adherence is actually taking the medication. Many adherence measures only focus on this step.[54, 55] But then patients must be vigilant and be aware of potential safety concerns and thus monitor regimen use in order to identify symptoms and seek appropriate action prior to an adverse event.[56] Studies by this team found that 54% of patients struggle to comprehend common warnings associated with medicines, and <10% routinely attend to this information.[57, 58] The final step is to sustain safe and appropriate medication use over time. Medications taken to treat chronic

conditions are often taken for a lifetime. Patients must come to terms with the need to constantly take medications, despite life events, attitudes and beliefs about medications.[16]

Adapting Health Systems via the Health Literate Care Model.

Koh et al. proposed a 'Health Literate Care Model' (derived from Wagner Care Model), which guides health systems in making targeted changes in the delivery of services to better engage patients in their care.[59] This is necessary, as improving health relies equally on patient and provider participation. But many patients have 'limited health literacy' and face difficulty when attempting to understand their health, act on medical instructions, and participate in self-care. Following this model, our intervention assumes all patients have information needs, large or small and could benefit from greater support around taking prescribed regimens. The Health Literacy Care Model, much like the Care Model[60], emphasizes the importance of a systems approach, and encourages changes to a health system that increases interactions between patients and providers. TAKE IT imparts the Health Literacy Care Model by: 1) implementing patient assessments to acquire feedback; 2) providing easy-to-understand, actionable medication adherence resources; 3) signaling to the transplant team via the EHR when concerns are noted.

Improving the Medication Use Process.

The Institute of Medicine (IOM) deconstructed the medication use process. There are several system failures that are salient root causes of poor adherence, medication errors, adverse drug events (ADEs), and sub-optimal treatment benefits. TAKE IT was designed to address these failures. At prescribing, problems with medication reconciliation are prevalent; as many as 67% of patients have inaccurate medication lists in their record.[48, 61] As a result, clinical decision making is less informed. Further down, counseling should coincide with treatment decision-making and ordering. This often does not occur, especially for side effects/risks. At Rx dispensing, the same concern for counseling exists. During the processes of self-administration and monitoring, our research has repeatedly shown a high prevalence of patient misunderstanding & errors.[48, 49, 53, 62]

2.7 Transplant Adherence in Kidney recipients by Engaging Information Technology.

Complex problems such as poor medication adherence require multifaceted solutions. Yet interventions must also be mindful of health system implementation and dissemination considerations in order for them to be sustained over time if found effective. Given the lack of available guidance from the literature specific to KT on adherence, we offer an evidence-based, medication adherence monitoring strategy that can activate available transplant center resources to intervene with patients earlier and prevent further complications.

3.0 Inclusion and Exclusion Criteria:

3.1 Methods of screening for eligibility

Patients will be initially screened for eligibility by the recruitment pulls at both sites. At Northwestern, a report will be created in the Electronic Data Warehouse (EDW) to identify patients within 24 months of KT, who are over 21 years of age. This report will contain the patient name, date of KT, phone number, nephrologist and date of upcoming clinic visits. At the Mayo Clinic, this report will be created in the patient database. For

subjects at Northwestern, a letter will be mailed to eligible participants on the list, notifying them that a research coordinator (RC) will be telephoning to invite them to participate in a study. Patients will be given the opportunity to opt out of being contacted by calling a hotline number and leaving a message. RCs will monitor the messages and remove patients who have chosen to opt out. Seven days after the letters have been sent, an RC will call patients who did not opt out to introduce the study, confirm eligibility, and screen for cognitive impairment, in alignment with the inclusion and exclusion criteria (3.2).

3.2 **Inclusion Criteria.** Patients will be screened for eligibility during an initial phone screener. They must meet the following eligibility criteria:

1) Patient is age 21 and older
2) Patient is within 5weeks-24 months of KT
3) Patient is English speaking
4) Patient is primarily responsible for administering own medication
5) Patient owns a cell phone and is comfortable receiving text messages
6) Patient has access and proficiency using internet at home

3.3 **Exclusion Criteria.** We will further refine the list of eligible patients during the screening and consent process to exclude those with

1) Severe, uncorrectable vision
2) Hearing impairments
3) Cognitive impairment

3.4 Adults unable to consent, individuals under the age of 21, and prisoners will be excluded from this research.

3.5 COVID-19 Survey Eligibility:
We will include any participant who has consented to participate in the main study and who has indicated that they were willing to be contacted for future studies by Dr. Wolf on the consent form.

4.0 Study-Wide Number of Participants:

4.1 700 patients will be eligible to be interviewed (n=350 per site).

5.0 Study-Wide Recruitment Methods:

5.1 Identification of potential participants

Northwestern University
To identify potential participants, a weekly pull of eligible patients will be reviewed by Research Coordinators (RC) at each site. At Northwestern, this report will include patient name, date of KT, phone number, address, medical record number (MRN), name of nephrologist and date of upcoming clinic visits. At Northwestern, this pull will be downloaded from the EDW. RCs will also review the Transplant Clinic Schedule in Epic to confirm upcoming appointments in the CTC. RCs will contact nephrologists to notify them about the study and to ask permission to contact all eligible patients for the study.

After obtaining permission from each nephrologist to contact patients, the Director of the Kidney Transplant Program, Dr. Leventhal will provide written permission for RCs to contact all eligible kidney transplant recipients for the study.

Mayo Clinic
At the Mayo Clinic, the RC will review transplant reports. With assistance from the nurse coordinator, RCs will review patient records to identify patients for potential recruitment that meet eligibility criteria.

5.2 Initial contact of potential participants

Northwestern University:

As per Northwestern policy, a letter will be sent to patients from Northwestern University detailing the study and notifying them that a research coordinator will be telephoning them to invite them to participate in the study. The letter will include a hotline number, which patients can call if they do not wish to be contacted for the study. Seven days after the letters have been sent, RCs will contact patients who did not opt out to introduce the study, to confirm eligibility and provide further information on the study. If the patient is eligible and interested, the RC will schedule the baseline interview around an upcoming clinic visit, where applicable. RCs will review the Transplant Clinic Schedule in Epic to confirm upcoming clinic visits in the CTC. Written consent will be obtained in person at the beginning of the baseline interview.

As part of a supplementary study leveraging TAKE IT patients (STU00209386), patients will be informed that they may be approached by a research coordinator from the Comprehensive Transplant Center during their upcoming blood draw and will have the option to consent to an additional blood draw. Participants will be informed that they can refuse to participate in the blood draw, without affecting their participation in the TAKE IT study. If the patient is interested in speaking with the IRB-approved coordinator, the patient's name, date of KT, study ID, and MRN will be shared with the study coordinator using a secured Sharepoint platform stored on the FSM drive.

Mayo Clinic:

In accordance with Mayo clinic policy, Daily Transplant List Report will be used to screen and identify de-novo (6 weeks post KT) subjects from the Mayo Clinic and Schedule Reports will be used to identify established (up to 24 months post KT) patients. Research Coordinators (RC) from the Mayo clinic will telephone identified patients from list asking for their participation and allowing them to opt out from being contacted further. Those

who are interested will be scheduled to meet with the RC to go over study requirements and provide signed consent.

6.0 Multi-Site Research:

6.1 All research activities will be conducted in the internal medicine ambulatory care practices affiliated with Northwestern University's Feinberg School of Medicine (Northwestern Medical Group), Northwestern Medicine Comprehensive Transplant Center (NMCTC), and Mayo Clinic Transplant Center. Together, these sites provide geographic and socioeconomic diversity among their patient populations ensuring optimal generalizability. All sites will be involved in the development or protocols and in data collection. Northwestern University will also be the data management site.

All in-person research interviews will take place in a private space within the study clinics at NMHC, NMCTC, and Mayo Clinic. Telephone calls with patients will take place in a private space at each site.

The University of Pennsylvania (UPenn) will be home to key research collaborators who will be involved in the study design, intervention development, and interpretation of results, but will not interact with patients and will not have access to data. Northwestern Memorial Health Care (NMHC) will be home to pharmacy collaborators who will be involved in the design and content of the intervention. They will also play a role in the follow-up component of the intervention.

Weekly meetings with all sites (Northwestern, Mayo Clinic, UPenn, NMHC) will be held throughout the study. This time will be used to discuss progress of the study and any changes to the protocol or study battery. The project manager will email any modifications to the IRB protocol to the team within one day of receiving approval. The project manager will hold weekly meetings with project staff to ensure that the protocol is being followed.

6.2 All required approvals will be obtained at each site prior to project implementation. In addition:

a. Once IRB approval is obtained at Northwestern University for study materials and protocol, Mayo Clinic will be sent approved materials via email. Northwestern will send Mayo Clinic any modifications made to be approved prior to implementation. Northwestern and Mayo Clinic will have regular conference telephone calls to discuss any problems and interim results, and to discuss any possible changes that need to be made to study materials and protocol.
b. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

7.0 Study Timelines:

7.1 We anticipate the entire study will take 5 years to complete. See study timeline below.

7.2 An individual patient will be involved in the study for a total of up to 24 months. They will complete a screener enrollment interview via phone, a baseline interview in-person and a 6-week and 6-month interview via phone. A 12-month and an 18 month interview will be conducted either in-person or over the phone*, with the remaining 24-month interview administered via phone. *If the 12-month interview cannot be done in person due to the timing of clinic visits, it will be done over the phone and we will attempt to do the 18 month interview in person.

7.3 We anticipate that patient enrollment will actively take place over 2.5 years. The date by which we expect to complete primary analyses is March 2021.

Table 2. Study Timeline

TASKS	Year 1				Year 2				Year 3				Year 4				Year 5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
PREPARATION PHASE:																				
Organize research team, convene DSMB	■																			
Protocol development at sites, train research team	■																			
Purchase laptops and software	■																			
Pilot test and refine assessment tools	■																			
Develop web portal, activate EHR tools & de-bug	■	■																		
Prepare SMS text service	■	■																		
Program database and laptop interface		■																		
Pilot TAKE IT		■																		
IMPLEMENTATION PHASE:																				
Recruit, consent, and randomize participants			■	■	■	■	■	■	■	■	■	■								
Conduct baseline interviews			■	■	■	■	■	■	■	■	■	■								
Implement Intervention			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Conduct follow up interviews					■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Seek process feedback from clinic staff								■				■				■				■
Extract EHR, pharmacy data							■				■				■				■	
EVALUATION PHASE:																				
Clean & analyze data					■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Summarize and interpret findings																	■	■	■	■
Provide feedback to sites																	■	■	■	■
Submit manuscripts for publication					■				■				■				■	■	■	■
Present findings at national venues					■				■				■				■	■	■	■

8.0 Study Endpoints:

8.1 The primary study endpoint will be the completion of all analysis of the Aims. A secondary study endpoint will be when all patient interviews are completed (n=700).

Table 4. Study Measures and Outcomes		Interview Timepoint				
Variable	Instrument(s) or Measure(s)	BL	6w	6m	12m	18m
Covariates		IP			IP	
Socio-demographics, patient characteristics	Age, sex, race/ethnicity, education, income, language, country of origin, time in US, others	■				
Health status (physical, mental)	Promis – anxiety & depression, global, physical	■				
Cognitive status	BTACT	■			■	
Social support	TSS; Medication Support Survey	■			■	
Health literacy	NVS, Chew	■			■	
Patient activation	CHAI	■			■	
Regimen characteristics	MRCI, drug class, cost	■		■	■	■
System Process Outcomes						
Receipt of UMS materials	Receipt of UMS (yes/no)		■	■	■	■
Medication reconciliation	Updates to medical/pharmacy records				■	
Receipt of SMS text reminders	Receipt of SMS (yes/no), satisfaction		■	■	■	■
Completion of assessment	Completion of assessment, satisfaction		■		■	
Clinic follow-up	Did clinic follow up on concerns		■		■	
Intervention impact on clinic practice	Qualitative interview with clinic staff					
Patient Effectiveness Outcomes						
Medication adherence	ASK-12, 24hr recall	■	■	■	■	■
	Pill Count	■		■		
	Proportion of Days Covered, Tacrolimus Levels			■	■	■
Treatment knowledge	General Rx knowledge, Demonstrated use, Consolidation	■	■	■	■	■
Quality of Life	PROMIS (physical, anx, dep, global)					
Clinical outcomes	Transplant related: eGFR, re-hospitalization, IFTA, acute rejection, toxicity, infection					
	Systolic blood pressure, Hemoglobin H1AC	■		■	■	
Cost Outcomes						
Programming maintenance costs for EHR	Printer ink, paper, staff time					
Running UMS technologies						
SMS monthly costs						

8.2 Covariates.

Patient Characteristics. We will include a socio-demographic/health questionnaire, the Tangible Social Support survey to assess the extent/quality of social connections[63], healthcare support will be measured using the Medication Support Survey. The Brief Test of Adult Cognition by Telephone (BTACT) and the Consumer Health Activation Index (CHAI) will also be included.[66]

Literacy Assessment: Newest Vital Sign (NVS). Patients are given a copy of a nutrition label and asked 6 questions about how they would interpret and act on the information. Scores are classified as high likelihood of limited literacy (0-1), possibility of limited literacy (2-3), and adequate literacy (4-6).[67]

Regimen Characteristics. Self-reported medications will be collected and grouped into drug class. These will capture important covariates that may be related to outcomes and unequally distributed among randomized subjects.

8.3 Fidelity (Process Measures).

Receipt of Mobile App reminders. At each follow-up, the RC will ask whether patients used the mobile app for medication reminders.

Use of Patient Portal. At each follow-up, the RC will inquire whether patients used the portal to complete the monthly adherence assessment. We will obtain data for the number of times a patient completes the assessment.

Care Alert Notification. We will review EHR data on care alerts, nurse follow up on portal-assessed adherence concerns. The RC will also ask patients if they received follow up, by whom, and what services were provided.

8.4 Effectiveness Outcomes. We will collect data on an array of knowledge, behavioral, and clinical outcomes.

Medication Adherence. Adherence will be measured using: 1) the Ask-12 Scale that assesses general medication attitudes and beliefs,[71, 72] 2) patient self-report of how many pills and how often each medicine was taken over the last 24 hours; 3) in-person and/or phone pill count using established guidelines employed by our team [R01HS00167; PI Wolf]; 4) a biologic measure using tacrolimus levels. For 24 hour recall, correct dosing will be measured as yes/no per drug, having properly shown dose (# pills), spacing (hours between doses), frequency (times per day), and total pills/day. For pill count, we will assess adherence within drug calls. If a patient fills a prescription for a drug in a class and then switches to another drug within the same class, all prescriptions will be summed in the numerator. Adherence will be treated both continuously and dichotomously (adherent ≥80%).[82,8374]

Biologic Measure. Medication adherence to IS medications will also be assessed by computing the standard deviation (SD) of a series of tacrolimus levels obtained for routine monitoring using validated methods.[75-79] Standard clinical practice at participating centers includes routine monitoring of tacrolimus levels. Tacrolimus levels obtained during acute illness will not be included in the SD calculation. This schedule should result in >30 levels in the first 6 months post KT, 12 levels in months 6-12, 6 levels in months 13-18, 6 levels in months 19-24; and 6-8 levels per year after the second year. Laboratory methods for measurement of whole blood levels are standardized, which should reduce variability between sites. SD calculations will be made using ≥4 levels obtained over 6 months based on availability. A higher SD indicates more variability between individual measures, and is highly correlated with less stable medication intake (non-adherence) and graft rejection.[75-77, 80] A SD of the mean levels of ≥ 2.5 will be indicative of non-adherence.[77, 81] This biologic measure of adherence will be calculated at 6 month intervals to correspond to interviews.

Composite adherence measure. Each individual measure of adherence has advantages and limitations, thus we will use multiple measures as recommended by experts.[16, 82] Maximum

likelihood estimation will be used to create a composite adherence metric by generating a single factor score from the 5 measures of adherence.

Regimen Knowledge: Patient identification of drug names and indication will be assessed via assessments used previously by Dr. Wolf and colleagues (ref). Patients will be asked about each of these via structured, open-ended items. Understanding of proper dosing will be assessed using the 24 hour recall task described above, but patients will be given credit if they demonstrate knowledge of how to take their medication correctly regardless of their actual behavior. From this assessment, we can also determine how patients are taking their entire multi-drug regimen, and if medications are consolidated in the most efficient manner. We will examine the total number of times throughout a 24 hour period patients indicate they will take medicine.

Quality of Life. We will use Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function, Anxiety, Depression and Global Health subscales [83-86].

Clinical Outcomes. will be collected via EHR by site. Transplant-specific outcomes include: 1) change in estimated glomular filtration rate (eGFR; ml/mn) over 24 months,[87] 2) *Re-hospitalization:* Acute care hospitalizations 3) *Acute Rejection:* proven biopsy meeting organ-specific Banff criteria;[88] 4) *Toxicity:* related to CNI medications (hypertension; neuro-toxic events);[11, 12] 5) *Infection:* CMV, BKV, bacterial infections assessed by laboratory tests and/or biopsies. *Blood pressure* (continuous SBP; control (y/n): SBP<140 & DBP<90) and g*lycemic control (HbA1c)* will also be examined in those with hypertension and diabetes.

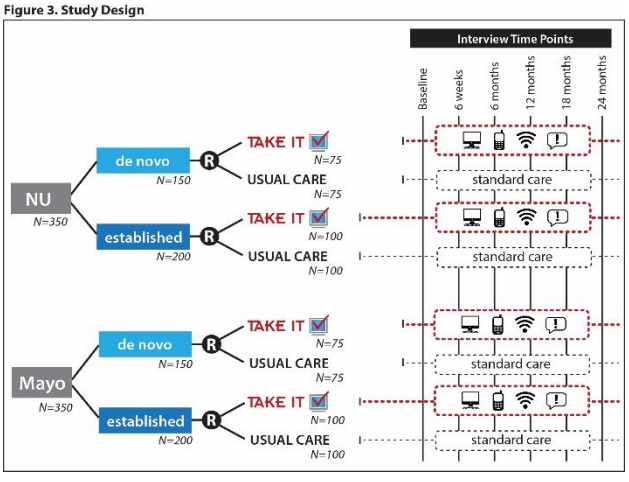
9.0 Procedures Involved:

Immediately at the onset of the project, we will organize the research team, finalize study procedures and data collection instruments, and design study databases. The PIs and Co-Is will share primary responsibilities for organizing key personnel and staff, plan study implementation, establish standard operating procedures per site, and to detail a plan for secure data collection/ transfer.

9.1 Overview & Study Design.

We will conduct a 2-arm, patient-randomized controlled trial at two large, diverse transplant centers (Northwestern University; Mayo Clinic). 700 KT recipients within 2 years of KT will be recruited and followed for 2 years (N=700 patients; n=350 per site; n=175 per study arm per site. Targeting both new and existing KT recipients is important, as adherence barriers may be different. As a result, we will aim to recruit patients

Figure 3. Study Design



with a wide spectrum of time since transplant, ranging from 5 weeks to 2 years post-transplant. In-person interviews will be conducted at baseline and 12 or 18 months (see **Figure 3**). To determine proximal effects of the TAKE IT strategy, a telephone interview will also be administered 6 weeks post-baseline. Follow-up telephone interviews will be conducted at 6, (12 or 18) and 24 months. Electronic health records will be ascertained to capture medication adherence measures and clinical outcomes (**Aim 1**). We will closely evaluate the implementation of all components of the TAKE IT strategy from launch through 2 years (**Aim 2**). Our evaluation includes several process outcomes to assess intervention reliability and sustainability (**Aim 3**). These findings will determine whether modifications to TAKE IT are necessary. Finally, we will further estimate the incremental costs of implementing and sustaining the TAKE IT strategy from the perspective of two transplant centers (**Aim 4**).

Research activities over the 5-year period will be divided into three phases: I) **Preparation** (Months 1-4); II) **Implementation** (Months 5-58), III) **Evaluation** (Months 13-60). In Phase I we will assemble our research team, orient sites, finalize study materials, and pilot test the TAKE IT strategy to ensure it is acceptable to patients, families, transplant clinicians and staff - making any necessary modifications. A randomized controlled trial will then be conducted and participants tracked for 2 years (Phase II). Our evaluation includes summative, process, and cost analyses to fully understand the clinical impact, feasibility, and costs of the TAKE IT strategy to guide dissemination efforts (Phase III).

9.2 Research Coordinator Training. A RC at each site will contact participants, engage in the consent process, conduct interviews, perform retention activities, follow-up with patients and perform quality assurance. Ms. Curtis will oversee project management, ensuring all research staff complete human subjects training (CITI); receive intensive interviewer training, led by Drs. Wolf and Ladner, as well as for safe data transfer. Training will highlight the sensitive nature of assessments. Simulations will monitor interviewer proficiencies.

9.3 Computer Programming. We will be using RedCap to collect all data. This allows for straightforward electronic entry of participant responses by the RC and generation of data files compatible with statistical programs. The database is both encrypted and password protected, and is only accessible by approved study personnel at Northwestern. Dr. Kwasny (analyst) will oversee the database structure and quality assurance activities.

9.4 Data Safety and Monitoring Board (DSMB). The DSMB will be formed early in the project and be given responsibility to review and approve the methods and analysis plan. It will be organized by Drs. Wolf and Ladner and include appropriate research methodologists and biostatisticians with related expertise. Meetings will be via video/tele-conference to review protocols, procedures, and concerns related to research integrity.

9.5 Trial Registration. We will register the trial protocol at ClinicalTrials.gov.

9.6 Implementation and de-bugging of Monthly Adherence Assessment and Care Alert Notifications. Due to changes to the hospital and ambulatory care practice electronic

health record (EHR) within the CTC, the PIs and Co-Is will plan the implementation of the EHR tools and web portal linkage within a modified RedCap platform. This will also facilitate use of the same platform at both sites. Dr. Ho oversees bioinformatics for the Transplant Center at Northwestern; both sites have dedicated programming support for this project to facilitate the modified build. Dr. Wolf has implemented the same processes to be tested in this study within GE Centricity, Epic and Cerner platforms; each build has included: 1) creation of an 'untethered' web portal site that can safely exchange medication information with the EHR; 2) use of the portal to assess medication adherence, and generate care alert notifications to the nurse coordinator via EHR based on survey responses. We have created a web-based assessment using RedCap, with Care Alert Notifications informed by responses in the assessment. An automated email functionality within RedCap will be used to generate care alert notifications to the nurse coordinator. The architecture for OTTR has already been mapped with support from Drs. Ladner, Ho and Abecassis, as well as input from the EDW programmer. Informatics analysts at both sites will implement all steps. The TAKE IT strategy will first be tested in the electronic test environment; we will troubleshoot and communicate with RedCap if necessary.

9.7 Randomization. Patient-level randomization will occur within site. At each site, 350 KT recipients (within 5 weeks-24 months of transplantation) will be randomized via a 1:1 scheme to intervention (TAKE IT) or usual care (n=175 per arm). The result will be 350 participants randomized to each study arm (N=700). Mr. Hur, working with Dr. Kwasny, will facilitate patient assignments via a random number generator application. Guided by Friedberg et al.20 we will blind: 1) personnel involved in statistical analyses (Dr. Kwasny, Mr. Hur), 2) principal investigators (Wolf, Ladner). Site project managers will have access to study arm assignments to initiate TAKE IT components to those randomized to receive them.

9.8 Clinic Space, Orientation and Workflow. Prior to implementation, Dr. Ladner will meet with surgeons, nephrologists, nurses, pharmacists and social workers at each of the sites to familiarize them with the planned study activities, answer questions, provide a printed synopsis of the protocol per site, and give contact information. They will work with Drs. Ho (Northwestern) and Sukuraman (Mayo) to coordinate site activities.

9.9 Research Procedures

Research activities will include a baseline interview, and follow-up interviews at 6 weeks, 6 months, 12 months, 18 months and 24 months. The baseline and either the 12 month or the 18 month interview will be conducted in-person*, while the remaining interviews will be conducted via phone. To facilitate the geographical diversity of KT patients at the Mayo Clinic, measures used in the baseline and 12 month interview can be administered in-person or via phone. If a pill count needs to be completed over the phone, a pill count tray will be sent to the participant prior to the scheduled interview.
*If the 12-month interview cannot be done in person due to the timing of clinic visits, it will be done over the phone and we will attempt to do the 18 month interview in person.

Pilot Testing and Refinement of Study Procedures. We will pilot test our strategy and study protocol, including the evaluation battery and patient materials, among 10 KT recipients per site who meet established patient eligibility criteria. Cognitive interviews (~45 min.) will be conducted to finalize and/or refine all study materials. We will 1) obtain average completion times for the interview, 2) elicit patient comprehension of the interview and intervention components. Necessary modifications will be made prior to full-scale implementation.

Baseline Interview. After confirming eligibility via phone, the RC will attempt to schedule the baseline interview to occur in person following an existing outpatient follow-up visit. RCs will review the Transplant Clinic Schedule in Epic to confirm upcoming appointments with the patients. At the baseline interview, the RC will re-introduce the study and obtain written consent, before administering the baseline interview. If a clinic visit is not scheduled, we will schedule interviews at the convenience of participants as necessary. Following the baseline interview, RCs will introduce the 'Transplant Hero' mobile application to participants with a smartphone. First, the RC will explain the app and its functionality in reminding patients to take their medications and provide educational information on KT medications. The RC will provide participants with the Transplant Hero Information Sheet. The RC will then ask the participant if they are interested in using the app as part of the study, and confirm that they have a smartphone (previously identified in initial screener and approach). If the participant is interested in downloading the app, the RC will assist in downloading the app. The RC will demonstrate entering a medication into the app, but will not enter the participant's entire regimen.

As part of a supplementary study leveraging TAKE IT patients (STU00209386), patients will be informed that they may be approached by a research coordinator from the Comprehensive Transplant Center during their upcoming blood draw and will have the option to consent to an additional blood draw. Participants will be informed that they can refuse to participate in the blood draw, without affecting their participation in the TAKE IT study. If the patient is interested in speaking with the IRB-approved coordinator, the patient's name, date of KT, study ID, and MRN will be shared with the study coordinator using a secured sharepoint platform stored on the FSM drive.

Follow-up Interviews. At Northwestern, an automatic reminder function built into Microsoft Access will alert RAs when to schedule follow-up encounters (6 weeks, 6, 12, 18, and 24 month interviews). Northwestern will send Mayo a weekly list of ID numbers and dates, prioritizing patients to schedule based on their windows. Each interview will take approximately 45-60 minutes, and subjects will receive $30 for baseline, 6 month and 12 month interviews, and $50 for the 18 month interview (total $140 compensation; none for 6 week or 24 month 20 minute phone interview).

9.10 Intervention: TAKE IT Strategy.

Our strategy is a multifaceted intervention that leverages the existing resources of a transplant center and increasingly available provider and patient-facing technologies to

simplify KT recipients' role in managing complex, multi-drug regimens and monitor use over time. The goal of the TAKE IT strategy is to optimize adherence and to detect problems earlier in order to improve health outcomes – both in transplant-specific conditions and for comorbidities. This approach is multifaceted, yet highly scalable due to minimal costs and impact on existing transplant center workflow. It includes the following 4 components:

1. **A routine adherence assessment** that requests patients to periodically report upon their medication use, providing a continuous link between the transplant center and patient beyond routine in-person visits. This assessment will routinely identify patients at risk of non-adherence and categorize the nature of their adherence concern in one of the following areas: cognitive, psychological, regimen, medical, social, economic.
2. **Care Alert Notifications** directed to the transplant center nurse coordinator if an adherence related problem is identified by the routine adherence assessment, who can then activate appropriate staff to respond.
3. **Quarterly adherence reports** that will automatically calculate a coefficient of variance for patients' tacrolimus levels at routine intervals and impart results to transplant nurse coordinators.
4. **Tailored clinical support** leveraging transplant center tools to directly target the adherence-related concern identified by the routine adherence assessment. The study team will focus on leveraging existing transplant center resources, including clinical consultation with pharmacists, social workers and transplant nurse coordinators, as well as existing technological and educational tools. These tools will be bundled and initiated in response to specific patient-reported adherence concerns.

9.11 Study Arms

Participants will be randomly assigned to either the TAKE IT strategy, as described in section 9.10 or usual care. Usual care refers to the normal standard clinical practices in place at either site, immediately post-transplant to the 5 years following. Northwestern and Mayo follow similar protocols for follow-up. KT recipients at both sites have lab values taken 3 times/weekly for the first 8-10 weeks post-transplant, shifting to weekly lab values for the next 3-4 months after, then monthly labs after. Both sites follow a similar tapering of weekly, to monthly to annual visits to the transplant nephrologist over the first 3 years. Protocol biopsies at both sites are taken between 3-6 months post-transplantation, at 12 then 24 months. All sites have a transplant nurse coordinator who has primary oversight of post-transplant care, full-time pharmacists and a clinical social worker. At Northwestern, the pharmacist has a standard visit with patients to review their prescribed regimen at discharge from the hospital. Social work and pharmacist visits are referrals as needed (PRN). At Mayo, both the pharmacist and social worker engage with patients only upon referral. Neither site has an active portal that engages KT recipients for any self-care support service.

9.12 Data Sources. Data sources for this study will include two in-person interviews and four phone interviews with participants, and Electronic Health Record chart review.

9.13 COVID-19 Survey.

From a pool of existing studies conducted by Dr. Michael Wolf (LitCog (STU00026255), REMinD (STU00203777), COPD Multimorbidity (STU00201640), UMS Portal (STU00201639), and TAKE IT (STU00204465), participants will be contacted and invited to participate in a one-time brief (5-10 minute) telephone survey to capture one additional outcome pertaining to their knowledge, attitudes, and beliefs about the COVID-19 outbreak in March 2020. They will also be asked a series of patient-reported health literacy items. Participants who complete to COVID-19 survey will receive a $10 gift card in the mail.

Recruitment will be done by phone by trained Northwestern RAs. We will contact anyone who has indicated that they were willing to be contacted for future studies run by Dr. Wolf on the consent form. Verbal consent will be obtained prior to completing the one time brief (5-10 minute) telephone survey.

Data from the COVID-19 survey and patient-reported health literacy items will be captured in REDCap.

10.0 Data and Specimen Banking:

10.1 Upon completion of all study activities, a final de-identified dataset will be created. This dataset will be stored indefinitely on the GIM server for secondary analyses. Only authorized personnel will have access to the dataset.

11.0 Data and Specimen Management:

11.1 Analysis Plan.

All analyses will be performed in SAS v9.4 (SAS Institute, Cary, NC). Mr. Hur will perform analyses under the direct supervision of Drs. Kwasny, Ladner and Wolf. Drs. Reese and Serper will also provide guidance.

Aim 1.

The proposed trial uses a 1:1 randomized design that assigns patients to TAKE IT or usual care within each cohort. We will accrue approximately 700 patients (350 de novo, 350 established) anticipating 90% retention in the de novo cohort (85% established) for follow-up at 1 year, leaving a minimum 525 patients for primary analyses. High retention will be supported through close follow-up, mailed reminders, birthday cards, and a newsletter. Given the clinical follow-up necessary for KT recipients, we are confident we will achieve this goal.

Regimen adherence at one year is the primary outcome of interest for Aim 1, with Rx knowledge and individual adherence measures also of primary interest. Secondary outcomes include quality of life (PROMIS outcomes and FKSI) and the clinical outcomes of change in eGFR, and any transplant-related re-hospitalization. Blood pressure control in those taking anti-hypertensive medications will also be examined. Relationships between

adherence and potential confounders (age, comorbidity, cognitive ability, regimen complexity, internet use, dose of intervention, etc.) will also be examined. For all outcomes, we will use generalized linear models (GLMs), adjusted for confounders and study site, specifying the logit link function for binary outcomes and identity link for continuous outcomes (quality of life, change in eGFR, SBP). Treatment group will be the independent variable of primary interest, with usual care specified as reference group. We will also include time since transplant at baseline (in months), baseline value of the outcome, and any potential confounding covariates noted in bivariate analysis. For outcomes measured per medication, a generalized estimating equation (GEE) approach will be employed to adjust standard errors for within-patient correlation. Should TAKE IT have an effect on outcomes, secondary analyses will examine if any of the potential confounders considered exhibit any effect modification.

Aim 2.

Generalized linear mixed models (GLMMs) will be used to examine intervention effects over the course of the study. Link functions will be included as described above for the GLM models. Adherence concerns may differ in the two cohorts, thus separate models will be employed for each cohort (de novo, established). Treatment group will be the independent variable of primary interest, modeled as a fixed effect with the usual care group specified as reference group. We will also include fixed effects for site (NU, Mayo), time since transplant (in months), and potential confounding covariates noted in bivariate analyses. Random participant effects for each participant will be included to account for repeated measurements nested within each participant (assuming a compound symmetry, although we will fit autoregressive structures as well, comparing fit using AIC and BIC criterion). Outcomes recorded at each interview will be analyzed by visit whereas adherence measured by tacrolimus levels, along with blood pressure control will be analyzed in 6-month intervals as described above. A time-since-transplant-by-arm interaction term will be included to examine if outcome trajectories/slopes over time differ by study arm. Since prescription knowledge and adherence will be assessed for each medication, 2-level GLMM will be used for these outcomes with medications nested in participants. For Δ eGFR and re-hospitalization outcomes, GLM models will be used since outcomes over 2 years are summarized in a single measurement. In the de novo cohort, change in eGFR from transplant to 2 years post-transplant and # hospitalizations (any hospitalization, if rare) within 2 years post-transplant will be modeled. For the established cohort, the time period for the both measures will span from transplant to 2-year study visit. It is possible those who do not complete the 2-year visit will differ in important characteristics (e.g. cognition, comorbidity), which could bias results. We will use collected data at prior interviews to understand the extent that individuals who complete follow-up differ from those who do not. If differences are found, pattern-mixture models will be employed by classifying participants' drop-out type or pattern (e.g. completed, refused, lost to follow up, death). This variable will then be added to mixed effects models to account for differences.[99, 100]

Power Calculation. The sample size calculation was based on the availability of 700 transplant patients estimated by the number of transplants conducted in 2012-2014 across the two sites. With the sample size set at 610 accounting for 85-90% retention at 1 year, we present the minimum differences we will be able to detect between the intervention and usual care arms for each outcome of interest. For the main outcome of medication adherence, we estimate 45% of the sample to be non-adherent using the composite score described above taking estimates for each individual measure into account.[19, 37] We will have sufficient power (≥ 80%) to detect differences of 11% in the entire sample assuming a 5% Type I error rate. Should TAKE IT be associated with potential confounders, calculations show that an R-squared of 0.2 between predictors (a conservatively high estimate under randomization), we would still maintain 70% power to detect the 11% difference. Although adjusting for confounders would decrease variability in adherence, and increase power. Detectable differences for individual adherence measures along with estimates and effect sizes for other outcomes of interest are listed in Table 5.[84, 87, 101-103]

Table 5. Detectable Differences in Health Outcomes between Study Arms at 1 Year

	Total (n=610) 305/arm		De Novo (n=270) 135/arm		Established (n=340) 170/arm	
Outcome	Usual Care Estimate	Minimum Difference	Usual Care Estimate	Minimum Difference	Usual Care Estimate	Minimum Difference
Primary Outcomes						
Rx Knowledge, %	50	11.3	60	15.9	45	15.1
Rx Non-adherence, %	45	11.0	35	15.2	50	15.0
Self-report, %	35	10.3	29	14.1	44	14.6
Objective (pill count), %	45	11.1	35	11.3	50	15.0
Claims (PDC), %	30	9.8	23	12.7	38	14.0
Biologic (SD Tacrolimus), %	40	10.8	30	14.3	45	14.7
Secondary Outcomes						
Quality of life, mean(SD)	46.2 (9.0)	2.0	45.8 (7.2)	2.5	49.5 (9.0)	2.7
Clinical outcomes						
Δ eGFR, mean(SD)*	-5.8 (9.0)	2.9	-3.0 (11.0)	3.8	-8.0 (15.0)	4.6
Re-hospitalizations, %	40	10.8	32	14.6	47	14.8
Systolic BP, mean(SD)**	136.7 (8.3)	2.2	138.3 (12.9)	5.1	135.0 (7.9)	2.8

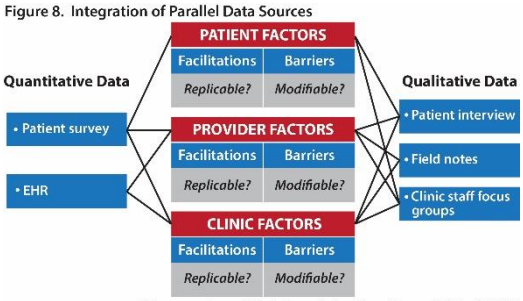
*Δ eGFR estimates over 2 years
**estimate 75% of cohort has hypertension (Total: n=458, 229/arm; De Novo: n=202, 101/arm; Established: n=256, 128/arm)

Exploratory Analyses. A single measurement for each exploratory transplant related clinical outcome (i.e. acute rejection, toxicity, infection) will be modeled at the end of the study indicating the total number of occurrences (or any for rare outcomes) over the course of the study using GLM models as described above. We recognize we likely will not have sufficient power to find differences in these outcomes. Intervention effects on blood pressure and glycemic control will be examined among those with diabetes and/or hypertension.

Aim 3.

We will determine the extent to which the interventions were implemented as planned at each site in order to optimize the intervention for future dissemination opportunities. Mixed methods will be employed using a convergent parallel design to obtain data on intervention implementation (Figure 8).[104] We will capture 4 data sources: 1) patient self-report, 2) EHR, 3) field notes, and 4) clinic staff. Patients receiving the TAKE IT strategy arm will be asked whether they received EHR materialsand visited the portal. We will examine if receipt of EHR tools increased KT recipient knowledge and behaviors. At 12 and 24 month interviews, a random sample of 50 patients from the intervention arm will be asked additional, semi-structured questions to explore 1) personal challenges with regimen adherence, 2) perceived value of the EHR, SMS, and

Figure 8. Integration of Parallel Data Sources



*Convergent parallel design adapted from Creswell & Clark, 2011

portal tools, 3) unmet needs and acceptability of other tools and approaches to support medication use. Interviews will be audio-recorded and transcribed. EHR data will capture whether patients actually receive EHR tools and if identified adherence concerns from the portal assessment generated a care alert, if a response was documented, and when. We will use field notes to monitor ongoing clinic changes. Ms. Curtis will have monthly calls with clinic administrators to document any changes that might have occurred and when. This includes relevant changes to clinic staffing, workflow, EHR, or any significant event that could potentially alter delivery and subsequent effectiveness of the TAKE IT strategy. Discussions groups will be held with staff during business meetings to assess the intervention's impact on workflow. These will be audio-recorded.

Analysis Plan. Quantitative and qualitative findings will be merged to answer 1) whether the intervention was implemented as planned (e.g. fidelity), 2) from a user-perspective, do interventions require modification and how. In this approach, both analyses are conducted separately and merged for side-by-side data comparisons.[104] For quantitative data (patient report, EHR data), frequencies will be generated to determine overall rate of perceived helpfulness of materials, receipt of materials, participation in the Web-based portal to report medication use, and the overall rate of EHR notifications. Although we expect a high fidelity level, if there are "glitches" that prevent TAKE IT from being implemented optimally, we will do an exploratory analysis to determine if fidelity rates had any association with improvement in outcomes. For qualitative data, we will review and explore the transcribed patient interviews and clinic staff discussions using content and ethnographic analysis led by Drs. Wolf, Ladner and Serper.[105, 106] Predetermined categories will organize feedback from all users: patient, provider, 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 (Figure 8). An additional layer within impeding factors would be whether factors are modifiable or not, and under facilitating factors, if they are replicable. Field notes and quantitative findings will be integrated. Transcribed interviews and field notes will be examined by Drs. Wolf, Ladner, & Serper independently. Analyses will be conducted with NVivo 10 (QSR International).

Aim 4.

Dr. Walton, working with Drs. Wolf, Ladner, & Reese will directly measure and assess the costs of developing and running the TAKE IT Strategy. The incremental cost of TAKE IT will be estimated relative to usual care from the perspective of the two sites implementing these processes and tools. The primary costs of running TAKE IT technologies in the EHR involve the limited expenses around printing (printer ink, paper, staff time) as a result of generating MedSheets and the Medlist with the AVS (during clinic visits). SMS monthly costs will be easily documented as well as usage. However, we will include estimates for programming maintenance for OTTR and Cerner EHRs, and the portal. We will test the sensitivity of results to changes in maintenance requirements (in programmer hours). Development costs for software and other programming requirements will be separately tracked based on programmer hours. Staff costs (nurse coordinator, pharmacist, social worker, other clinicians, programmer) will be measured using tracked time spent on the intervention and wage estimates. We will test the sensitivity of operational costs to different assumptions about potential use of variable staff using different salaries but

assuming the same proficiency in terms of time required. We will also assess the sensitivity of estimates to different proficiency levels that could arise from learning by doing.

11.2 Protocol to ensure confidentiality.

Each subject will be tracked using an Access database. Each site will have a separate Access database built using the same template. The databases, containing identifiers and other related information for coordinating research activities (recruitment outcome, interview call log and interview visit schedule, etc.) will be kept on the secure Northwestern and Mayo Clinic network drives respectively. Only the PI, project manager, and RCs at each site will have access to this database.

Data will be collected via RedCap. RedCap is a secure, encrypted online data collection tool, which can only be access by NU authorized personnel listed on the project's IRB. An affiliate Northwestern Net ID will be generated for the RC at Mayo Clinic to enable data entry for Mayo participants. Data access groups will be identified so NU interviews cannot access to Mayo's data and vice versa.

Several methods will be employed to reduce the risk of breach of confidentiality. A study identification number will be assigned to each subject in the study. The research data collected and stored will have the study identification number and no other identifying information on it. The consent forms and the de-identified study data will be kept in a separate locked file cabinet. Using this method, if someone were to gain illegal access to the locked filing cabinet with study data, they would have no way to link this data to any identifying information.

11.3 Quality Assurance.

Training will begin after surveys and interview protocols have been refined and standardized. A training session will be conducted by Drs. Wolf and Ladner at each site. The training will include tailored discussion of 1) roles and responsibilities; 2) HIPAA and IRB mandates (completion of Human Subjects Training Program - CITI; 3) effective recruitment communication and interviewing with attention paid to health literacy and culture; and 4) gathering and recording data including administering the structured survey electronically. Role playing will be used to fine tune training for obtaining informed consent and interviewing patients. Institutional Review Board (IRB) approval will be attained at both sites prior to any active recruitment efforts. All interviewers will be required to demonstrate competence in survey administration.

11.4 Study-wide data management.

Data collected includes patient consent forms, data gathered using the EDW and Transplant Report pulls, and data collected during the study interviews.

<u>COVID-19 Survey Data</u>

By extending existing studies conducted by Dr. Michael Wolf (LitCog (STU00026255), REMinD (STU00203777), COPD Multimorbidity (STU00201640), UMS Portal

(STU00201639), and TAKE IT (STU00204465) to capture an additional patient-reported outcome related to one's knowledge, attitudes and behaviors related to COVID-19, we can link participants' responses to this cross-sectional survey to a minimum data set of participant characteristics that include demographic, socioeconomic, cognitive (including health literacy) and health behavioral characteristics. We will then be able to investigate determinants of COVID-19 knowledge, attitudes and behaviors without duplicating data collection efforts for these variables.

Data Access. The Data Custodian is the Principal Investigator, Dr. Michael Wolf. Only authorized personnel listed on each institutions IRB will have access to the data. Any information that could allow identification of individual participants, including the master list, will be kept strictly confidential.

Local Data Storage. Data will be stored in REDCap, a secure, web-based application, and on the Northwestern and Mayo Clinic secure servers for the length of the study. RCs at Mayo Clinic will be provided with an affiliate Northwestern id in order to be granted access to NU's REDCap system. RCs will be assigned to their own Data Access Group which restricts access to their subject's records. Each group is blinded to all other data/records. For the purposes of creating a clinic alert notification, intervention patients' name, DOB and MRN will be entered into RedCAP and sent to pre-identified clinical staff via RedCAP survey function to Northwestern email addresses. For Mayo Clinic patients, name, DOB and MRN will also be entered into RedCAP and sent to pre-identified clinical staff via RedCAP to Mayo clinic email addresses. The name, DOB and MRN will be stored in the Mayo Clinic Data Access Group, which will not be visible to any Northwestern staff. Only the RC at the Mayo Clinic will have access to this data in the RedCap Data Access Group.

The Project Manager or Data Analyst will download the de-identified data only for both sites from REDCap monthly and save to the "Analytic" folder within the TAKE IT project folder on the FSM department servers which are located in a HIPAA compliant data center. These data files do not contain any identifiable information, and are identified by project staff by an assigned study ID. All identifiable information for Northwestern patients will remain in the secure REDCap system. Upon completion of all study activities, a final de-identified dataset will be created and all identifiable information will be deleted. This dataset will be stored indefinitely on the GIM server for secondary analyses. Only authorized personnel will have access to the dataset. All identifiable information will be deleted upon completion of the study

Data Transfer to Data Coordination Site. All survey data collected at the Mayo Clinic site will be stored in REDCap and downloaded by the Northwestern project manager or data analyst monthly. For the purposes of creating a clinic alert notification, intervention patients' name, DOB and MRN will be entered into RedCAP and sent to pre-identified clinical staff via RedCAP survey function to Mayo Clinic email addresses. The name, DOB and MRN will be stored in the Mayo Clinic Data Access Group, which will not be visible to any Northwestern staff. Only the RC at the Mayo Clinic will have access to this data in the RedCap Data Access Group. Northwestern staff will only have access to de-identified

study data from Mayo Clinic. De-identified data from both sites will be combined into a master dataset. A back-up copy of all transferred data will be maintained at Mayo Clinic.

12.0 Provisions to Monitor the Data to Ensure the Safety of Participants:

12.1 Data Safety and Monitoring Board (DSMB). The DSMB will be formed early in the project and be given responsibility to review and approve the methods and analysis plan. It will be organized by Drs. Wolf and Ladner and include appropriate research methodologists and biostatisticians with related expertise. Meetings will be via video/tele-conference to review protocols, procedures, and concerns related to research integrity.

13.0 Withdrawal of Participants:

13.1 In the case that subjects are unresponsive for 6 months past the date their follow up interview was due, they will be labeled as 'lost to follow up' and will be withdrawn from the study.

13.2 Participants can choose to withdraw from the study at any time. If a participant chooses to withdraw from the research, any data collected up until the point of withdrawal will still be utilized as it will not include identifying information.

14.0 Risk to Participants:

14.1 Participation in the study poses minimal risk of psychological, social and economic harm. Informing subjects in advance that they may decline to answer any questions asked during the interview and discussion group will mitigate any risks associated with expressing their opinions (e.g., feeling uncomfortable). They will also be assured they can terminate their participation in the study at any time without penalty. The risk/benefit ratio is low. Minimal to no risk is expected for subjects in this study.

15.0 Potential Benefits to Participants:

15.1 It is possible that subjects enrolled in the intervention study arms may directly benefit in that they may have, as a result of this study, a better functional understanding of their medication. The results of this study may provide important information regarding how strategies can be implemented via the EHR and mobile and computer technologies to support safe and appropriate medication use.

16.0 Vulnerable Populations:

N/A

17.0 Community-Based Participatory Research:

N/A

18.0 Sharing of Results with Participants:

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

19.0 Setting:

19.1 Mayo Clinic Arizona. The Mayo Clinic Transplant Center in the greater Phoenix, AZ area provides comprehensive evaluation, medical and surgical treatment, and follow-

up care for patients with ESRD who may be in need of a KT. The Mayo Clinic Arizona, Minnesota, and Florida campuses perform more KTs than any other institution in the U.S. At the Arizona site, they have dedicated clinical research staff involved in multiple renal transplantation clinical trials including immune-suppressive drug studies and immune monitoring trials. This infrastructure will aid Dr. Heilman & Sukumaran in conducting the study.

19.2 Northwestern University. Northwestern Medicine Comprehensive Transplant center (NMCTC) is the largest center for kidney transplantation in Illinois and is a leader in research, innovation and patient care in the Midwest. There are 4 satellite offices outside of Chicago, in Illinois and Indiana, to assure evaluation services closer to patients' homes. This is the largest living donor kidney transplant program in the country. It is also one of the most experienced facilities in steroid-free KT. With the Northwestern University Transplant Outcomes Research Center, led by Dr. Ladner, we have one of the only health services research teams in transplant.

19.3 All in-person research interviews will take place in a private space within the study clinics at NMHC, NMCTC, and Mayo Clinic. Telephone calls with patients will also take place in a private space to ensure patient confidentiality.

20.0 Resources Available:

20.1 This study is led by senior health services researchers with expertise in health literacy, medication adherence, use of EHR and consumer technologies, patient safety in transplant, and complex research designs. Additionally, the project staff have worked on similar research projects and have adequate training to carry out the proposed study.

This study is being conducted with patients from clinics within Northwestern Medical Healthcare (NMHC), Northwestern Medicine Comprehensive Transplant Center (NMCTC), and Mayo Clinic. All physicians within the practice will be informed of the study.

21.0 Prior Approvals:

21.1 National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)

22.0 Recruitment Methods:

22.1 Identification of potential participants

Northwestern University

To identify potential participants, a weekly pull of eligible patients will be reviewed by Research Coordinators (RC) at each site. At Northwestern, this report will include patient name, date of KT, phone number, address, medical record number (MRN), name of nephrologist and date of upcoming clinic visits. At Northwestern, this pull will be downloaded from the EDW. RCs will contact nephrologists to notify them about the study and to ask permission to contact all eligible patients for the study. After obtaining permission from each nephrologist to contact patients, the Director of the Kidney Transplant Program, Dr. Leventhal will provide written permission for RCs to contact all eligible kidney transplant recipients for the study.

Mayo Clinic
At the Mayo Clinic, the RC will review transplant reports. With assistance from the nurse coordinator, RCs will review patient records to identify patients for potential recruitment that meet eligibility criteria.

22.2 Initial contact of potential participants

Northwestern University:

As per Northwestern policy, a letter will be sent to patients from Northwestern University detailing the study and notifying them that a research coordinator will be telephoning them to invite them to participate in the study. The letter will include a hotline number, which patients can call if they do not wish to be contacted for the study. Seven days after the letters have been sent, RCs will contact patients who did not opt out to introduce the study, to confirm eligibility and provide further information on the study. If the patient is eligible and interested, the RC will schedule the baseline interview around an upcoming clinic visit, where applicable. RCs will review the Transplant Clinic Schedule in Epic to confirm upcoming appointments with the patients. Written consent will be obtained in-person at the beginning of the baseline interview.

Mayo Clinic:

In accordance with Mayo clinic policy, Daily Transplant List Report will be used to screen and identify de-novo (6 weeks post KT) subjects from the Mayo Clinic and Schedule Reports will be used to identify established (up to 24 months post KT) patients. Research Coordinators (RC) from the Mayo clinic will telephone identified patients from list asking for their participation and allowing them to opt out from being contacted further. Those who are interested will be scheduled to meet with the RC to go over study requirements and provide signed consent.

22.3 Recruitment procedure
Recruitment will be completed over the phone by CITI-certified Northwestern Research Coordinators (RCs) and Mayo Clinic RCs as applicable per site. RCs will call eligible patients to confirm eligibility and provide further information on the study. If the patient is eligible and interested, the RC will schedule the baseline interview around an upcoming clinic visit, where applicable. Written consent will be obtained in-person at the beginning of the baseline interview.

Training will begin after questionnaire and interview protocols have been refined and standardized. The PIs and project manager will lead sessions to orient the research staff to the surveys and study protocols (e.g., interview process, use of laptop PCs, data security). All interviewers will be required to demonstrate competence in survey administration. All interviews will be conducted via REDCap, a secure, web-based application. Recruitment outcomes along with identifiable data necessary to contact participants will be recorded in NU's REDCap. Interviews will be conducted by research coordinators (RCs) over the phone and in-person. RCs will read each question aloud and record patient responses

directly onto a password protected laptop or PC computer using REDCap. Study interview data does not contain any identifiable information, and are identified by project staff by an assigned study ID. All identifiable information will remain in the secure REDCap system. Contacts with enrolled participants outside of in person interviews will be made via USPS and telephone.

22.4 Payment for Participation

Research Interview	Payment	Form of Payment
baseline	$ 30	cash at close of interview
6 weeks	$ 0	(brief, included in other interviews)
6 month	$ 30	money order mailed via USPS
12 month	$30	cash at close of interview
18 month	$50	money order mailed via USPS
24 month	$0	

COVID-19 Survey: Participants who complete the COVID-19 survey will receive a $10 gift card in the mail. All participants who verbally consent and complete any portion of the telephone interview will be compensated

23.0 Number of Local Participants:

23.1 A total of 350 participants will be enrolled locally (n=700 study-wide) for patient interviews.

24.0 Confidentiality:

24.1 Data Access.

The Data Custodian is the Principal Investigator, Dr. Michael Wolf. Only authorized personnel listed on each institutions IRB will have access to the data. Any information that could allow identification of individual participants, including the master list, will be kept strictly confidential.

24.2 Local Data Storage.

Data will be stored in REDCap, a secure, web-based application, and on the Northwestern and Mayo Clinic secure servers for the length of the study. RCs at Mayo Clinic will be provided with an affiliate Northwestern id in order to be granted access to NU's REDCap system. RCs will be assigned to their own Data Access Group which restricts access to their subject's records. Each group is blinded to all other data/records. For the purposes of creating a clinic alert notification, intervention patients' name, DOB and MRN will be entered into RedCAP and sent to pre-identified clinical staff via RedCAP survey function to Northwestern email addresses. For Mayo Clinic patients, name, DOB and MRN will also be entered into RedCAP and sent to pre-identified clinical staff via RedCAP to Mayo

clinic email addresses. The name, DOB and MRN will be stored in the Mayo Clinic Data Access Group, which will not be visible to any Northwestern staff. Only the RC at the Mayo Clinic will have access to this data in the RedCap Data Access Group.

The Project Manager or Data Analyst will download the de-identified data only for both sites from REDCap monthly and save to the "Analytic" folder within the project folder on the FSM department servers which are located in a HIPAA compliant data center. These data files do not contain any identifiable information, and are identified by project staff by an assigned study ID. All identifiable information will remain in the secure REDCap system in designated Data Access Groups visible only to authorized staff at Northwestern University for Northwestern patients and the Mayo Clinic for Mayo patients. Upon completion of all study activities, a final de-identified dataset will be created. This dataset will be stored indefinitely on the GIM server for secondary analyses. Only authorized personnel will have access to the dataset. All identifiable information will be deleted upon completion of the study.

All survey data collected at the Mayo Clinic site will be stored in REDCap and downloaded by the Northwestern project manager or data analyst monthly. For the purposes of creating a clinic alert notification, intervention patients' name, DOB and MRN will be entered into RedCAP and sent to pre-identified clinical staff via RedCAP survey function to Mayo Clinic email addresses. The name, DOB and MRN will be stored in the Mayo Clinic Data Access Group, which will not be visible to any Northwestern staff. Only the RC at the Mayo Clinic will have access to this data in the RedCap Data Access Group. Northwestern staff will only have access to de-identified study data from Mayo Clinic. De-identified data from both sites will be combined into a master dataset. A back-up copy of all transferred data will be maintained at Mayo Clinic.

24.3 Data Transfer to Data Coordination Site.

All survey data collected at the Mayo Clinic site will be stored in REDCap and downloaded by the Northwestern project manager or data analyst monthly. For the purposes of creating a clinic alert notification, intervention patients' name, DOB and MRN will be entered into RedCAP and sent to pre-identified clinical staff via RedCAP survey function to Mayo Clinic email addresses. The name, DOB and MRN will be stored in the Mayo Clinic Data Access Group, which will not be visible to any Northwestern staff. Only the RC at the Mayo Clinic will have access to this data in the RedCap Data Access Group. Northwestern staff will only have access to de-identified study data from Mayo Clinic. De-identified data from both sites will be combined into a master dataset. A back-up copy of all transferred data will be maintained at Mayo Clinic.

24.4 Data Collected.

The proposed research will include data from 600 patients. Participants will be interviewed at baseline, 6 weeks, 6 months, 12 months, 18 months, and 24 months at Northwestern University and Mayo Clinic. The final data set will include patient socio-demographic characteristics, health status, health literacy and motivation, medication knowledge and

adherence behaviors, as well as clinical outcomes (change in eGFR, re-hospitalization, acute rejection from biopsy, etc.). The primary outcome is medication adherence at year 1. Any identifying information (e.g. personal and/or contact information) will be kept separate from other data; all information will be kept in secure, password protected files.

25.0 Provisions to Protect the Privacy Interests of Participants:

25.1 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). In order to preserve participants' confidentiality rights, research subjects will be assigned code numbers that will be used to identify all the information collected. Using these codes, none of the collection forms will contain the names of the participants. All electronic data will be stored in on a password-protected computer. A Microsoft Access master study tracking database will contain information linking participants to their study id numbers. This database will be encrypted and kept on a secure server and only accessible by study personnel.

Survey data will be stored in a REDCap. Individual study identification numbers will be assigned to each participant and only this number will appear on the survey. For the purposes of creating a clinic alert notification, intervention patients' name, DOB and MRN will be entered into RedCAP and sent to pre-identified clinical staff via RedCAP survey function to Northwestern email addresses. For Mayo Clinic patients, name, DOB and MRN will also be entered into RedCAP and sent to pre-identified clinical staff via RedCAP to Mayo clinic email addresses. The name, DOB and MRN will be stored in the Mayo Clinic Data Access Group, which will not be visible to any Northwestern staff. Only the RC at the Mayo Clinic will have access to this data in the RedCap Data Access Group.

Subjects will be told that unless required by law, only the study investigators, members of the project staff, the funding agency and representatives of Institutional Review Boards will have the authority to review any study records. In such cases, these parties too will be required to maintain confidentiality. The final data set will be stripped of identifiers. Data will be shared via presentations at national and international meetings and in peer reviewed publications. Furthermore, all results will be shared with the funding institute.

25.2 Participation in the study poses minimal risk of physical, psychological, social and economic harm. Informing subjects in advance that they may decline to answer any questions asked during the interview will mitigate any risks associated with expressing their opinions (e.g., feeling uncomfortable).

25.3 All enrolled participants will provide written consent, include HIPAA authorization for the collection of all data, including review of the patient's medical record.

25.4 Only authorized personnel listed on each institutions IRB and approved by the PI will have access to the data.

26.0 Compensation for Research-Related Injury:

N/A

27.0 Economic Burden to Participants:

N/A

28.0 Consent Process

28.1 Written consent will be obtained for all participants, prior to their participation. The consent process will take place in a private clinic space within NMHC, NMCTC, and Mayo Clinic. Participants will be provided with a consent form by the RC, who will ask the participant to read the consent form in full. Once complete, the RC will reiterate the key aims and participant requirements (2 in-person and 4 phone interviews), before giving the participant the opportunity to ask any questions they might have. The participant will be informed that they are free to withdraw at any time without penalty and all information will be provided to the subjects in terms that they can fully understand. There will be no exertion of any overt or covert coercion.

28.2 Verbal consent process for COVID-19 survey: Subjects will be informed about the nature of the study by a CITI-certified RC and asked to provide verbal consent. They will be informed that they may withdraw from the study at any time and given contact information for the PI and RC. A verbal consent, or a waiver of documentation of consent, is deemed appropriate because the nature of the study involves minimal risk and no PHI will be collected. If a patient agrees to participate after the RC reads the consent, the RC will record the patient's name on the consent form and the RC will sign their own name on the form. These consent forms will be locked in a file cabinet only accessible to necessary research staff. Patients will be given the option to receive a blank consent form for reference if they request it.

29.0 Process to Document Consent in Writing

Written consent will be obtained for all participants, prior to their participation. The consent process will take place in a private clinic space within NMHC, NMCTC, and Mayo Clinic. Participants will be provided with a consent form by the RC, who will ask the participant to read the consent form in full. Once complete, the RC will reiterate the key aims and participant requirements (2 in-person and 4 phone interviews), before giving the participant the opportunity to ask any questions they might have. The participant will be informed that they are free to withdraw at any time without penalty and all information will be provided to the subjects in terms that they can fully understand. Once the RC is satisfied that the participant understands the consent process and the nature of their participation in the research study, the participant will be asked to sign and date the consent form. Participants will receive a second signed consent form for their records. After the interview, signed consent forms will be stored in locked cabinets in General Internal Medicine.

30.0 Drugs or Devices:

N/A

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