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## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| (S)AE | (Serious) Adverse event |
| AMBS | Adolescent Medication Barrier Scale |
| ATR | Allocation of Treatment Responsibility |
| ATR-C | Allocation of Treatment Responsibility – Caregiver |
| AYA | Adolescent and young adult |
| DSMB | Data safety monitoring board |
| GEE | Generalized estimating equations |
| GFR | Glomerular filtration rate |
| KT | Kidney transplant |
| SB | Spina bifida |
| PI | Principal investigator |
| SES | Socioeconomic status |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| WTH | Way to Health |
| BET | Behavioral Economics Theory |
| BRIEF | Behavior Rating Inventory of Executive Function |
| CIC | Clean Intermittent Catheterization |
| CKD | Chronic Kidney Disease |
| ESRD | End-stage Renal Disease |
| KOSB | Knowledge of Spina Bifida |
| UDS | Urodynamic Studies |
| CV | Coefficient of Variation |
| QLS | Quasi-Least Squares |
| DCC | Data Coordinating Center |
| UPenn | University of Pennsylvania |
| PMACS | The Penn Medicine Academic Computing Services |
| SQL | Structured Query Language |
| NA | Non-adherence |
| PMBS | Parent Medication Barrier Scale |
| SOSBMR | Sharing of Spina Bifida Management Responsibilities |
| UTI | Urinary Tract Infection |
| WHO | World Health Organization |
| CHOP | The Children's Hospital of Philadelphia |
| mhealth | Mobile Health |
| Participant/Subject | Refers to the child age 12-24 with KT or SB, NOT the parent/legal guardian |

## TABLE1: SCHEDULE OF STUDY PROCEDURES – ARM 1 AND ARM 2

<table>
<tr><td>Phase</td><td>Run-in</td><td>Intervention</td><td colspan="3">Follow-up</td></tr>
<tr><td>Duration</td><td>2 weeks</td><td>6 months</td><td>2 months</td><td>2 months</td><td>2 months</td></tr>
<tr><td rowspan="3">Both Arms</td><td colspan="5">$10 for withdrawals who complete an OPTIONAL Exit Survey within 5 days.</td></tr>
<tr><td>Complete of baseline surveys and $20 lump sum for adherence reporting.<br><br>$20 if baseline surveys are completed within 5 days and $10 if baseline surveys are completed in 6 – 10 days</td><td>Access to Way to Health portal with educational modules and personal dashboard to see adherence progress. Complete surveys after six months post.<br><br>$20 if post intervention surveys are completed within 5 days and $10 if post intervention surveys are completed in 6 – 10 days.</td><td colspan="3" rowspan="2">No further access to Way to Health portal.<br><br>$2/week for adherence reporting.<br><br>Complete surveys six months post.<br><br>$20 if post follow-up surveys are completed within 5 days and $10 if post follow-up surveys are completed in 6 – 10 days.</td></tr>
<tr><td>Arm 1</td><td>(not randomized yet)</td><td>$2/week for adherence reporting.</td></tr>
<tr><td rowspan="2">Arm 2</td><td rowspan="2">(not randomized yet)</td><td rowspan="2">Adherence progress sent to phone by text with personalized feedback on performance. $10/week if</td><td colspan="3">Adherence progress sent to phone by text with weekly personalized feedback on performance.</td></tr>
<tr><td>$10 every 2 weeks if adherence goal met over</td><td>$10 every 4 weeks if adherence goal met over</td><td>No further “extra” incentive.</td></tr>
</table>

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|---|---|---|---|---|---|
| | | adherence goal met. | 2 week average. | 4 week average. | |

# 1 BACKGROUND INFORMATION AND RATIONALE

## 1.1 Introduction

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has funded a cooperative agreement including six leading pediatric renal transplant and spina bifida (SB) care centers in the United States, the Children's Hospital of Philadelphia (CHOP), Boston Children's Hospital, Children's Healthcare of Atlanta, Seattle Children's Hospital, Lurie's Children of Chicago, and Children's Mercy Kansas City.

The overarching goal of this five-year, phase II, randomized clinical trial is to improve poor long-term health outcomes in both adolescents and young adults (AYA) with either a kidney transplant (KT) or spina bifida (SB), respectively. More specifically, this study will focus on decreasing premature allograft loss in subjects with kidney transplant (KT) due to medication nonadherence and kidney damage in subjects with SB due to urinary non-continence. To achieve these goals, this study will implement a real-time feedback system, Way to Health (WTH), that will provide education and support, increase awareness and incentivize positive health behavior, in addition to standard of care. Further, this study will investigate the mechanisms of behavior change by examining the role of financial incentives, positive feedback and the relationship between the two. The study will compare two cohorts of KT and SB subjects, which will undergo varied levels of financial incentives and positive feedback. Data from KT and SB subjects will be analyzed separately. This innovative mobile health (mhealth) strategy will improve our current measures of adherence and increase our understanding of factors that influence adherence for two AYA populations, KT and SB subjects, respectively. Our study will contribute novel insight to inform the design of future interventions targeting persistence of behavior change and can be used in other centers and for other chronic disease groups.

## 1.2 Name and Description of Investigational Product or Intervention

The study intervention will use the WTH web-based platform to support AYA with KT or SB as they navigate their daily treatment burdens. This will be achieved via bi-directional text messaging, including the sending of reminders and positive feedback by WTH and the messaging of pictures of medication or catheter in hand at time of treatment by the participant. This intervention will assess sustainability of this novel bi-directional messaging system and the impact of providing education and support, increasing awareness and incentivizing positive health behavior in real-time.

## 1.3 Findings from Clinical Studies

Kidney Transplant: AYA with KT have lower five year allograft survival than any other age group besides patients over 65 years of age, and once diagnosed with rejection, they do not respond as well to treatment, with fewer complete rejection reversals and greater residual graft dysfunction.[2-4] High rates of non-adherence (NA) play a key role in high rates of rejection, premature allograft dysfunction and graft failure.[5-8] AYA KT recipients who experience graft failure are twice as likely to be NA (OR 2.07, 95% CI 1.12-4.06).[9] Recent evidence also demonstrates a significant association between NA and development of de novo donor-specific antibody.[10] AYA who develop donor-specific antibody wait substantially longer for

re-transplantation.[11] Thus, nonadherent AYA with KT are primed to spend less of their lifetime with a functioning graft and more time on dialysis, leading to tremendous loss in quality of life and increased co-morbidities and astounding economic burden.[12] After the first year post-transplant, Medicare costs for patients with a functioning graft are $30,000 annually, less than half the annual costs of dialysis care.[2] Persistent NA leads to over $21,000 in increased adjusted medical costs over 3 years per patient, with AYA less than 24 years of age having the highest rates of persistent NA.[9]

Spina Bifida: SB is one of the most common and disabling birth defects, occurring in 3.1 of every 10,000 live births.[13] Despite dramatic advances in our understanding and treatment of SB, the lower urinary tract outcomes for patients with SB continue to show urodynamic patterns consistent with neurogenic bladders.[14] Bladder dysfunction, if not treated, leads to kidney damage and failure. Clean Intermittent Catheterization (CIC) remains a critical component of medical treatment to achieve urinary continence and optimize bladder function.[15] Recognizing that the risk for kidney damage can often be significantly reduced or eliminated with close monitoring and medical treatment, the CDC has established a protocol to standardize bladder and kidney assessments starting from infancy.[16] Yet, even with better assessments, patient continence cannot be achieved without rigorous adherence to treatment regimens. Health professionals and patients with SB both rate adherence to catheterization as highly problematic.[17,18] When patients do not succeed in achieving urinary continence with medical management, surgical reconstruction, with bladder augmentation or creation of a catheterizable stoma, may be needed. However, these procedures incur significant secondary complications, including increased risks of urinary tract infection (UTI), urolithiasis, metabolic abnormalities, cancer and bowel perforation.[19]

Patients with SB experience rates of inpatient admissions with UTI that are over 50 times higher than the general population.[20,21] It is estimated that if the number of UTI hospitalizations among SB patients were reduced by half, $4.4 million would be saved per 1000 patients.[20] Among SB patients who progress to end-stage renal disease (ESRD), ESRD is usually caused by urological complications and is reached at a substantially younger age compared to patients without SB (41 vs. 62 years, $p<0.001$). ESRD increases the already high complexity of SB care, and consequently, AYA with SB face tremendous difficulties in accessing care, contributing to reduced access to transplantation.[22] Thus, similar to AYA KT recipients, AYA with SB are primed to spend more of their lifetime on dialysis, leading to tremendous loss in quality of life, increased co-morbidities and increased costs. In addition, the incontinent AYA is more likely to remain socially isolated and disengaged.[23] These significant burdens of cost and quality of life emphasize the crucial need to support AYA with KT and SB in their ability to comply with treatment regimens.

### 1.4 Relevant Literature and Data

NA in chronic conditions is a particularly challenging problem to solve primarily because: 1) adherence is a complex behavior that requires long-term engagement and 2) adherence is difficult to measure.

NA is often considered a patient-driven problem and, as a consequence, many interventions focus solely on the patient. However, The World Health Organization (WHO) has emphasized that this perception fails to acknowledge that many external factors influence people's behavior and their capacity to adhere to prescribed treatments.[24] The WHO Multi-Dimensional Adherence Model identifies five interrelated categories of risk factors for NA: social and economic, condition-related, treatment-related, patient-related and healthcare system factors.

These five elements provide an excellent framework for conceptualizing barriers and facilitators to treatment adherence in AYA with KT and SB. In addition to the economic burdens of chronic illness, social factors, such as family conflict and lack of cohesion, are associated with NA. Children with SB and KT tend to lag behind typically developing youth in general independence, and their parents are more likely to be overprotective.[17] This dynamic often contributes to family conflict as adolescents with SB emerge into adults.[17,25] There are also important condition-related factors that result from the effects of underlying chronic illness. Neither chronic kidney disease (CKD) nor SB is an isolated condition. The co-morbidities associated with these diseases increase adherence burden, by augmenting the number of treatments, labs and doctors' visits. Neurocognitive dysfunction is also common among AYA with SB and KT, which results in increased learning challenges.[26,27] AYA with KT and SB experience many treatment-related factors as well. Immunosuppressives and catheterization have many unfavorable side effects. Treatment complexity, particularly in terms of numbers of medications or frequency of treatments, impairs adherence.[28,29] Patient-related factors include low self-esteem, low self-efficacy and social adjustment difficulties. Patients who are more self-motivated and perceive greater control over their health tend to be more adherent.[28] AYA with chronic conditions do not want to appear different from their peers and often struggle accepting their healthcare needs because they do not feel "normal".[30-32] Further, AYA who have overprotective parents may not receive the practice and encouragement needed to gain confidence and skills to become autonomous in their care.[17] Lastly, the healthcare system poses barriers to treatment adherence. Factors linked to NA include limited time providers spend with patients, lack of information about health and treatments, and little focused discussion of adherence barriers.[33]

Historically, interventions to address NA have been limited to enhanced monitoring with increased lab screening and clinic visits to provide supplemental education and counseling.[34-36] This approach has been met with limited success, largely because clinic-based interventions increase patient and caregiver burden, for families who are already overwhelmed with tasks at hand. Moreover, education alone is not sufficient to promote long-term patient engagement in health-promoting behavior[37]; most patients know what they need to do to stay healthy but they face everyday challenges in doing so.[24]

Another great challenge in designing adherence interventions is that there is no "gold standard". No single measure of adherence shows high sensitivity and specificity.[38] Current methods of adherence measurement are fraught with feasibility challenges. Shemesh and Fine suggest the ideal measure of adherence should: a) be easily integrated into practice, b) pose minimal additional burden to patients c) be simple d) correlate with adverse clinical outcomes and e) identify nonadherence in real time.[39] To date, no adherence interventions have

successfully achieved these goals for KT recipients. Adherence research in SB is even more limited. Some insight has been gleaned regarding adherence barriers for AYA with SB and there is evidence that cathing adherence declines over time. However, few adherence interventions have been tested in AYA with SB, and among those, a caregiver questionnaire has been the primary assessment used.[1,17] Thus, for AYA with SB, there remains very little understanding of day-to-day treatment adherence patterns and challenges.[40]

**Mobile Technology: Well-Suited to Address Current Gaps in Adherence Interventions for AYA**

Mobile technology presents a novel opportunity to transform AYA participation in their own healthcare, creating a space for AYA with KT or SB to practice autonomy in healthcare self-managements skills and receive feedback on performance. Mhealth interventions that use mobile technology, such as apps or texting, have shown early promise in acceptability and feasibility as an adherence tool for AYA across a wide range of chronic conditions.[18,41,42] Using texting as a mode of intervention is low-cost, highly available and uniquely allows ecological momentary assessments, i.e. assessments and interventions are provided when patients need support the most - at the time behavior is performed. Text messaging interventions pose minimal burden, are simple and can identify nonadherence in real-time.

**Innovation in Theoretical Framework**

Behavioral economics theory (BET) starts with empirical observations that humans often behave in predictably irrational ways. BET endorses theory-driven interventions that make it easy for subjects to do what is in their best interests and harder to do what is not. BET targets the human tendency toward present bias, counteracting long-term negative outcomes which are often heavily discounted.[37] Incentive motivation is another key construct. Behavioral economics also targets regret aversion, the desire to avoid regret or loss. In BET intervention models, subjects are often told what they could have gained if they had performed the positive health behavior. This approach promotes motivation to avoid loss of a reward in the future. BET models have been rigorously tested and shown to be effective across a wide range of adult chronic disease conditions[43-45], but BET has not been widely applied in AYA.

Bandura's social cognitive theory, an important theoretical framework for behavioral economics, suggests that behavior can be changed through new learning experiences, guidance in the adjustment of perceptions, and support for the development of capacities.[57] Bandura identified increased self-efficacy as a common mechanism to promote behavior change. Methods for increasing self-efficacy include: 1) helping subjects gain mastery of behavior, 2) showing subjects that others like them can do it (social modeling), 3) improving physical and emotional states by reducing stress and fear and 4) persuading through encouragement.[46] BET relies heavily on effective feedback loops that incorporate these methods.

Our study will pair financial incentives with positive text messages. Although the use of financial incentives is common in children in everyday parenting, i.e. allowances, there has

been limited use in research. In two pediatric studies, giving children small incentives to increase healthy food consumption more than doubled fruit and vegetable intake, and effects were sustained for two months.[47,48] Another study recently showed that giving young adults with food allergies $10 a week for carrying epinephrine auto-injectors was more effective in increasing carriage than text reminders alone.[49] Our study will be the first to test the effects of paired text messages with small incentives to promote adherence among AYA with KT or SB.

**Innovation in Methods**

Bi-directional texting has shown good acceptability in other AYA populations.[41,49,50] In a small study of AYA with HIV, increased adherence reported by interactive text messaging showed a trend toward positive improvements in biomarkers.[41] Co-investigator, Lisa Schwartz, has applied interactive text messaging in THRIVE 2.0, a randomized clinical trial to improve healthcare self-management skills in AYA cancer survivors, with very low refusal rates (<20%) and 90% study retention.[51]

### 1.5 Compliance Statement

This study will be conducted in full accordance with all applicable Research Policies and Procedures and all applicable federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 2 STUDY OBJECTIVES

The purpose of this study is to determine the effectiveness of behavioral feedback plus economic incentives to promote treatment adherence among a large diverse population of AYA with KT or SB.

### 2.1 Primary Objective

The primary objective is to compare the efficacy of two 6-month mhealth-based interventions to promote treatment adherence among AYA with KT or SB. In Arm 1, subjects will receive text reminders and a nominal weekly payment for participation. Arm 2 is an enhanced, tailored intervention with individualized feedback on adherence behavior and financial incentives for meeting adherence goals. The primary outcome is change in proportion of time adherent between run-in and 6-month intervention. Adherence data will be collected in real-time when subjects take pictures of their medicines (or catheter) in hand. Secondary outcomes are coefficient of variation (CV) in immunosuppressive drug levels for KT recipients and change in bladder wall compliance for SB subjects. Hypothesis 1: Adherence will be higher during the 6-month intervention in Arm 2 vs. Arm 1.

## 2.2 Secondary Objective

The secondary objective is to evaluate differences in sustainability of adherence in a 6-month post-intervention period in which financial incentives are tapered then stopped in Arm 2. We will compare the change in adherence from the intervention's end to 6 months post-intervention. Hypothesis 2: Arm 2 (vs. Arm 1) will demonstrate greater sustained adherence as incentives are slowly removed due to ongoing tailored feedback.

## 2.3 Tertiary Objective

The tertiary objective is to identify psychosocial correlates of adherence changes in AYA with KT and SB. Using validated surveys, we will examine perceived barriers, self-efficacy and healthcare responsibility before and after the 6-month intervention and follow-up periods. Hypothesis 3: Positive change in adherence behavior is associated with positive changes in self-efficacy, reduced perceived barriers and increased healthcare responsibility.

## 2.4 Quaternary Objective

The quaternary objective is to evaluate differences in comorbidities and demographic data of lost to follow up participants to that of those who complete the study intervention. This will contribute to understanding generalizability.

# 3 INVESTIGATIONAL PLAN

## 3.1 General Schema of Study Design

### 3.1.1 Screening Phase

Potential subjects in the Nephrology, Urology and Spina Bifida outpatient clinics will be screened using the protocol inclusion and exclusion criteria. Those who meet the criteria will be approached by a member of the study team at their regularly scheduled clinic visit or by phone and asked if they would like to hear about the study. If the subject expresses interest, he or she will have an orientation to the WTH platform facilitated by the research coordinator. The research coordinator will help subjects open an account, sign an informed consent, and complete a baseline questionnaire at study entry during a clinic visit. At this enrollment visit, coordinators will explain the bi-directional texting and smartphone adherence reporting to participants and show them how to perform the reporting. Participant phones will be checked to ensure texting and camera capabilities. If a participant does not have a smartphone, a study phone will be provided. Coordinators will also give each participant a Greenfire Clin Card, explaining to the participant how the card works. A member of the Data Coordinating Center (DCC) research staff will activate each card remotely. If participants are pressed for time, they may complete the baseline questionnaires via the WTH platform and will be requested to do so within five days of study entry. Participants who complete their surveys within this time frame will receive $20. Participants who complete their surveys within 6 – 10 days will receive $10. They will be sent a text reminder to complete their questionnaires if they have not done so within five days. Coordinators will tell participants that they can earn either a water bottle

or a phone wallet at baseline for the completion of surveys within this time. They will be given this prize in clinic if they are able to complete all baseline surveys during the clinic visit. If not, they will be mailed their prize.

Additionally, the research coordinator will help a parent/legal guardian set up his/her WTH portal. The parent/legal guardian will sign an informed consent and also complete a baseline questionnaire. Through this portal, parents/legal guardians will have access to educational information, a copy of the consent form and the ability to answer questionnaires when prompted. The IRB has waived consent and HIPAA authorization for the child's absent parent/legal guardian in the case that both parents/legal guardians are not present at time of enrollment. The waivers will occur for the purpose of collecting demographic information about the absent parent/legal guardian, such as income and education level. If both parents/legal guardians are present then both will be consented.

An iPad will be provided to each site by the DCC for ease of facilitating this phase in clinic.

After the informed consent process, a medical history and medical record review will take place.

### 3.1.2 Run-In and Intervention Phase

During the first two weeks (run-in period) after questionnaire completion, all participants will be asked to take a photo of their medicines or catheter in hand at the time of treatment without prompts from Way to Health. The photo will be automatically transmitted to WTH and time stamped to record treatment adherence. Coordinators will emphasize that these data will be used to collect baseline information on the routine adherence behavior of AYA with KT and SB, and these data will not be reported to healthcare providers. Participants will receive $20 (to be administered via Greenfire Clin Card), given as a lump sum at the end of the 2-week period. Participants can track payments in the WTH portal.

After the run-in period, coordinators will call participants to explain the randomization process. Participants will be told that WTH will randomly assign them to one of two groups and will notify them of their status by text. Participants will either be assigned to 1) access personal weekly adherence reports by logging into the WTH website or 2) receive weekly adherence reports automatically to their smartphone with direct feedback on their performance. Participants will also be told that they will receive ongoing weekly compensation for adherence reporting, but that the compensation structure will change and vary by group during the intervention so that we can learn more about the role of financial incentives for AYA.

**Study Arms:** At 2 weeks, a computerized randomization scheme will be generated by WTH to assign participants to one of two arms, stratified by disease group (KT or SB), and age category (12-17 vs. 18-24). User written code in Stata 14.0 will utilize a block randomization scheme that, within each disease/age group stratum stratification, first randomly orders blocks of size 2 and 4 and then randomly orders subjects within blocks. Due to the nature of the study, blinding of participants and research staff is not possible. However, the relying site PI's will

be blinded. WTH will send a text to each participant explaining the compensation scheme. Participants will be asked to reply yes to confirm receipt and willingness to participate. Additionally, coordinators will call participants at the time to explain the intervention and answer any questions. Subjects will be randomized as follows:

**Arm 1:** Participants will begin to receive daily text messages as reminders and continue to report real-time treatment adherence with photos. They will receive $2/week to encourage real-time adherence reporting. Pay is not contingent on meeting a target adherence score, but only on submitting at least one photo per week. In addition to the payments, participants will be able to log in to WTH to see their personal dashboard with a visual display of their weekly adherence performance. They will also be able to access educational resources related to their primary disease. Educational materials for KT recipients will include web links to participant resources specific for AYA, including resources publicly available through the American Society of Transplantation, National Kidney Foundation and the United Network for Organ Sharing and educational videos created by CHOP's care team.[52-54] The major transplant themes that will be covered include: medication management, infection precautions, energy and physical activity, mental health and social adjustment, nutrition, sexuality and risk behavior education, and vocational resources. Similarly, educational materials for the SB subjects will be drawn from web-based AYA-specific resources, including web links to the Centers for Disease Control Living with Spina Bifida Program and the National Spina Bifida Association.[55,56] The major SB themes that will be covered include: bladder and bowel management, infection precautions, skin health, physical health, mental health and social adjustment, nutrition, sexuality and risk behavior, safety and vocational resources. All of the educational materials that will be used have been vetted by healthcare professionals, but every resource will be reviewed and adapted by the investigative team to ensure relevance, currency, accuracy and readability. Every month, participants will receive a text encouraging them to visit the WTH educational modules and to check their earnings. WTH is able to track usage of the modules by individual. Parents/legal guardians will have access to these same educational materials via their own WTH portals. Additionally, to mitigate the minimal risk of this study, parents/legal guardians will be notified if their child is excessively non-adherent.

**Arm 2:** Participants randomized to Arm 2 will also begin to receive daily text messages as reminders and report real-time treatment adherence with photos, and will have web access to the educational modules through the WTH portal. Similarly, every month, participants will receive a text encouraging them to visit the WTH educational modules and to check their earnings. In contrast to Arm 1, they will receive their weekly performance results by text to their phone with tailored feedback, e.g. "Congratulations. You performed your cathing every time you needed to this week. Cathing regularly helps you prevent infections and keeps your kidneys healthy. Keep up the strong work!" or "You took your medicines on time 3 out of 4 times this week. Taking medicines can be hard. Check out the WTH link on tips for improving your timing (with URL inserted). Hang in there!" In Arm 2, participants will not receive $2/week for adherence reporting during this 6-month intervention phase. Instead, they will receive a larger incentive of $10/week if they perform their desired treatment behavior at least 85% of the time. Incentive notification will be texted to participants: "Congratulations. You earned $10 for your hard work being consistent with cathing/taking your medicine. Way to take care of yourself!" or "You just missed earning $10 this week. You were really close. If

you remember just two more times next week, your hard work will pay off with $10 in your pocket and better health."

Text messages will be gain-framed, i.e. will focus on what the participant has accomplished vs. what he/she has not. The text message bank for U-REAACT will be adapted from Dr. Lisa Schwartz' prior texting intervention with AYA cancer survivors (THRIVE: Texting Health Resources to Inform, Motivate and Engage) which has an established repository of over 120 positively-framed motivational health messages.[51]

Similarly to Arm 1, parents/legal guardians will have access to the same educational materials via their own WTH portals. Additionally, to mitigate the minimal risk of this study, parents/legal guardians will be notified if their child is excessively non-adherent.

At the end of the intervention phase, participants and parents/legal guardians, again, will complete the baseline questionnaires. Participants who complete their surveys within 5 days will receive $20. Participants who complete their surveys within 6 – 10 days will receive $10.

### 3.1.3 Follow-up Phase

Six months after randomization, participants will receive a message that the main study intervention is ending but that we will continue to track their adherence reporting to understand the benefits of the study. At this time, all participants and parents/legal guardians will repeat the baseline questionnaires. Arm 1 will continue to receive reminders and report their daily adherence with mobile phone camera photography and earn $2/week for reporting, but they will no longer have access to their WTH portal, i.e. no visualization of dashboard or educational modules. Arm 2 will be told that incentives will be tapered. They will no longer be able to access the WTH portal. Arm 2 participants will get $2/week for reporting during this follow-up period and will continue to receive weekly adherence feedback texted to them. They will be eligible to receive an additional $10 for meeting their adherence target of $\geq 85\%$ over a lengthened time interval. Specifically, they will receive feedback and $10 every 2 weeks x 4 (if goal is met over average of preceding 2 weeks), then $10 every month x 2 (if average monthly goal is met) then no incentive (beyond the $2/week for reporting) for the last two months. At the end of the follow-up phase, participants and parents/legal guardians, again, will complete the baseline questionnaires. Participants who complete their surveys within 5 days will receive $20. Participants who complete their surveys within 6 – 10 days will receive $10.

Parents/legal guardians will no longer have access to their WTH portal during this phase, but will still receive messages if their child is excessively non-adherent.

### 3.1.4 Study Staff Involvement

Beyond enrolling and helping set up WTH portals, coordinators and/or study staff will phone participants at the time of randomization, at the end of six months and end of follow-up period to answer any questions. Coordinators and/or study staff will also contact participants if they fail to report adherence for more than 3 days in a row to assess barriers, such as technical

issues, etc. The DCC research staff will pay participants monthly by uploading earnings to their Clin Cards. Research staff will confirm the participant has possession of his/her Clin Card prior to loading the card with the money earned

## 3.2 Allocation to Treatment Groups and Blinding

Subjects will be randomized to Arm 1 or Arm 2 via a computerized randomization scheme generated by WTH to assign participants to one of two arms, stratified by disease group (KT or SB), and age category (12-17 vs. 18-24). User written code in Stata 14.0 will utilize a block randomization scheme that, within each disease/age group stratum stratification, first randomly orders blocks of size 2 and 4 and then randomly orders subjects within blocks. Lead investigators at each site will be blinded to which Arm their participants are in. The research staff must know which participants are in which Arm in order to appropriately manage each participant.

## 3.3 Study Duration, Enrollment and Number of Sites

### 3.3.1 Duration of Study Participation

The study duration per subject will be 12.5 months, with a 2-week run-in, 6-month intervention and 6-month follow-up.

### 3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at CHOP, Boston Children's Hospital, Children's Healthcare of Atlanta, Seattle Children's Hospital, Lurie's Children of Chicago, and Children's Mercy. CHOP will act as the DCC.

We will recruit 3 cohorts. Cohort one and two are the KT and SB subjects, respectively. Cohort three is the parent/legal guardian(s) of those enrolled in cohort one and two. Recruitment will stop when 200 total subjects are recruited in both cohort one (KT) and cohort two (SB), respectively. It is expected that approximately 400 subjects will be enrolled between the two cohorts to produce 180 evaluable KT and 180 evaluable SB subjects. Approximately 50 KT and 50 SB participants will be recruited at each of the four centers. Recruitment for cohort 3 will stop when 800 parent/legal guardian(s) are recruited. Recruitment of the parent population will be dependent upon the recruitment of cohorts one and two. Up-to 200 parents/legal guardians may be recruited at each of the four centers.

## 3.4 Study Population

Subjects 12 to 24 years of age and their legal parent/guardian(s) will be recruited from the Nephrology, Urology and Spina Bifida clinics at CHOP, Boston Children's Hospital, Children's Healthcare of Atlanta, Seattle Children's Hospital, Lurie's Children of Chicago, and Children's Mercy.

### 3.4.1 Inclusion Criteria

1) Males or females age 12-24 years.
2) KT subjects must be greater than 3 months post-transplant.
3) SB subjects must be able to perform CIC as part of their treatment.

4) Able to speak and read in English.
5) Willing and able to provide informed assent or consent.
6) Parental/guardian permission (informed consent) if appropriate.

### 3.4.2 Exclusion Criteria

1) Unwilling to participate.
2) Unable to speak or read in English.
3) Unable to provide informed assent or consent.
4) Severe cognitive impairment, as reported by treating team in recruiting clinic.
5) On dialysis
6) Acquired post-transplant lymphoproliferative disease less than one year prior to enrollment
7) Less than 3 months post-transplant.
8) Unable to perform CIC.
9) Prescribed Immunosuppressive medications once per day.
10) Provider recommendations of CIC once per day

Parents/legal guardians meet the inclusion criteria if their child is eligible for the study. Parents/legal guardians will be excluded if they meet one or more of items #1-4 of the above exclusion criteria. Subjects that do not meet all of the enrollment criteria may not be enrolled. If a subject's parent is unwilling to participate, the subject may still enroll in the study. In this case, clinical information about the parent, such as household income and education level, will not be collected. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

# 4 STUDY PROCEDURES

## 4.1 Screening Visit

Using the WTH web-based research portal, a research coordinator will help subjects and their parents/legal guardians open an account, electronically sign an informed consent and complete a baseline questionnaire. The baseline questionnaire will include the surveys listed in section 5.2.1 Diagnostic Tests, Scales, Measures, etc. as well as a general demographics questionnaire. The coordinator will explain the WTH portal, and set-up text reminders with the participant's input.

### 4.1.1 Run-In Period

During this two-week period, all participants will send a photo of their medicine or catheter in hand at time of treatment to the WTH phone number provided at enrollment. Participants will receive $20 (to be administered via Greenfire Clin Card), regardless of their adherence score, given in a lump sum at the end of the run-in period.

## 4.2 Study Treatment for Arm 1

### 4.2.1 Intervention Phase

Participants will receive daily text messages as reminders and continue to report real-time treatment adherence with photos. They will receive $2/week to encourage real-time adherence reporting. Pay is not contingent on meeting a target adherence score, but only on submitting at least one photo at time of treatment per week. In addition, participants will be able to log in to WTH to see their personal dashboard with a visual display of their weekly adherence performance and educational materials relevant to their disease group. Parents/legal guardians will have access to these same educational materials via their own WTH portals. Additionally, to mitigate the minimal risk of this study, parents/legal guardians will be notified if their child is excessively non-adherent. This portion of the study will last for 6 months. At the end of this phase, participants and parents/legal guardians will be asked to answer the baseline questionnaires again. Participants who complete their surveys within 5 days will receive $20. Participants who complete their surveys within 6 – 10 days will receive $10.

### 4.2.2 Follow-Up Phase

After 6 months, participants will receive a message that the main study intervention is ending. At this time, participants and parents/legal guardians, if applicable, will be prompted to complete the baseline questionnaires again. Arm 1 will continue to receive reminders and report their daily adherence with mobile phone camera photography and earn $2/week for reporting. Parents/legal guardians will continue to be notified if their child is excessively non-adherent. Parents/legal guardians and participants will no longer have access to their WTH portal during this period. This portion of the study will last for 6 months. At study completion, participants and parents/legal guardians will be asked one final time to answer the baseline questionnaires. Participants who complete their surveys within 5 days will receive $20. Participants who complete their surveys within 6 – 10 days will receive $10.

## 4.3 Study Treatment for Arm 2

### 4.3.1 Intervention Phase

Participants randomized to Arm 2 will also begin to receive daily text messages as reminders and report real-time treatment adherence with photos, and will have web access to the educational modules through the WTH portal. In contrast to Arm 1, they will receive their weekly performance results by text to their phone with tailored feedback. In Arm 2, participants will receive $10 per week for adherence reporting during this 6-month intervention phase if they perform their desired treatment behavior at least 85% of the time. Incentive notification will be texted to participants based on their adherence behavior. Parents/legal guardians will have access to these same educational materials via their own WTH portals. Additionally, to mitigate the minimal risk of this study, parents/legal guardians will be notified if their child is excessively non-adherent. This portion of the study will last for 6 months. At the end of this phase, participants and parents/legal guardians will be asked to answer the baseline questionnaires again. Participants who complete their surveys within 5 days will receive $20. Participants who complete their surveys within 6 – 10 days will receive $10.

### 4.3.2 Follow-Up Phase

After 6 months, participants will receive a message that the main study intervention is ending. At this time, participants and parents/legal guardians will be prompted to complete the baseline questionnaires again. Arm 2 will be told that incentives will be tapered. Parents/legal guardians and participants will no longer be able to access the WTH Portal. Arm 2 participants will get $2 per week for reporting during this follow-up period and will continue to receive weekly adherence feedback texted to them. Parents/legal guardians will continue to be notified if their child is excessively non-adherent. They will be eligible to receive an additional $10 for meeting their adherence target of $\geq$ 85% over a 2 week period x 4 (as opposed to one week during the intervention period). The incentive will then become $10 every month for two months (if the average monthly goal is met), and finally no incentive beyond the $2 per week for reporting. This portion of the study will last for 6 months. At study completion, participants and parents/legal guardians will be asked one final time to answer the baseline questionnaires. Participants who complete their surveys within 5 days will receive $20. Participants who complete their surveys within 6 – 10 days will receive $10.

## 4.4 Study Staff Check-Ins

Study staff will phone participants at the time of randomization, at the end of six months and end of follow-up period to answer any questions. Study staff will also contact participants if they fail to report adherence for more than 3 days in a row to assess barriers, such as technical issues, etc.

## 4.5 Subject Completion/Withdrawal

Study subjects may withdraw from the study at any time for any reason without prejudice to their care. If a participant who has been randomized chooses to withdraw, a study member will send them a link to the Exit Survey. If the participant completes the Exit Survey within five days of receiving the link, the participant will be paid $10 as a thank you for their time.

# 5 STUDY EVALUATIONS AND MEASUREMENTS

## 5.1 Screening and Monitoring Evaluations and Measurements

### 5.1.1 Medical Record Review

- Date of birth
- Weight and height
- Demographic data including age, race, gender, education level, insurance status, household income, possession of a 504/IEP plan, languages spoken at home, living arrangement and accessibility to care
- Medical history, including reason for transplant, time since transplant, etiology of renal or hepatic disease, age at initial diagnosis, history and length of preceding dialysis, baseline GFR, transplant complications, and delayed graft function
- Chart review in EPIC will be updated every 6 months from study entry for each

subject. For kidney transplant recipients, chart review will include immunosuppressive drug levels, hospitalization events, rejection episodes, graft failure events, biopsies and serum creatinine, number of medications, number of pills and other clinically relevant data. For spina bifida subjects, chart review will include level of lesion, type of spina bifida, number of shunt surgeries, ambulation method, other co-morbidities, baseline bladder capacity and compliance, route of catheterization, history of urinary tract infection, number of medications, frequency of catheterization and other clinically relevant data.

- No biopsies or any other medical procedures beyond standard of care will be done solely for this study. Study staff will review clinical biopsy results when chart reviews are completed.

## 5.2 Efficacy Evaluations

### 5.2.1 Diagnostic Tests, Scales, Measures, etc.

All surveys will be administered and entered directly by and into the WTH portal. The KT and SB subjects will complete the same baseline executive function measure, perceived adherence barriers, and self-efficacy scale. Since few other forms have been validated in both disease groups, KT and SB participants will complete different forms measuring healthcare responsibility & disease knowledge. The forms parents/legal guardians will complete are indicated below. Surveys will be completed at enrollment, end of intervention and study completion.

Both KT and SB subjects will complete:

- Behavior Rating Inventory of Executive Function – Adult (BRIEF-A) for participants over 18 & parents will complete BRIEF2-Parent (BRIEF-P) if the subject is <18 years of age

- Adolescent Medication Barrier Scale (AMBS) & parents will complete Parent Medication Barrier Scale (PMBS)

- Self-Efficacy for Managing Chronic Disease 6-Item Scale

- Way to Health Exit Survey – to be completed at withdrawal or study completion

Only KT subjects will complete:

- Allocation of Treatment Responsibility (ATR) & parents will complete the Allocation of Treatment Responsibility – Caregiver (ATR-C)

- Heart Transplant Knowledge questionnaire (adapted for KT)

Only SB subjects will complete:

- Sharing of Spina Bifida Management Responsibilities - Child (SOSBMR-C) parents

will complete the Sharing of Spina Bifida Management Responsibilities – Parent (SOSBMR-P)

- Knowledge of Spina Bifida (KOSB)
- SB Barriers and Cathing Barriers Measure

| Item Measured | Forms for KT Group | Forms for SB Group |
|---|---|---|
| Executive Function | BRIEF-Adult; BRIEF2-Parent | BRIEF-Adult; BRIEF2-Parent |
| Perceived Adherence Barriers | AMBS/PMBS | SB Barriers and Cathing Barriers Measure |
| Self-Efficacy | Self-Efficacy For Managing Chronic Disease 6-item Scale | Self-Efficacy For Managing Chronic Disease 6-item Scale |
| Treatment Responsibility | ATR; ATR-Caregiver | SOSBMR-Child; SOSBMR-Parent |
| Knowledge of Condition Assessment | Heart Transplant Knowledge Questionnaire (adapted for KT) | KOSB |
| Efficacy of Way to Health Portal | Way to Health Exit Survey; Way to Health Exit Survey - Parent | Way to Health Exit Survey; Way to Health Exit Survey - Parent |

### 5.2.2 Survey Descriptions

- Adolescent/Parent Medication Barriers Scale (AMBS and PMBS) is a 17-item scale that examines perceived barriers to medication adherence, in 3 categories: Disease Frustration/Adolescent Issues, Ingestion Issues, and Regimen Adaptation/Cognitive Issues. AYA answer questions on a Likert scale, from “strongly disagree” to “strongly agree,” with higher scores representing a greater amount of perceived barriers to treatment. For KT subjects < 18 years of age, parents will complete a parallel parent-specific survey (PMBS). The PMBS measures the same 3 factors, plus a Parent Reminder item. Results of these surveys will be recorded in the WTH study database.

- Allocation of Treatment Responsibility (ATR and ATR-Caregiver)**:** all participants will complete the ATR; their parents will complete the ATR-Caregiver. The ATR questionnaire helps to identify who is responsible for the medication taking routine and how those responsibilities are divided between the subject and their parent/ caregiver(s). The ATR is a 3 part questionnaire: Part 1: General Information on treatment responsibility, Part 2: Report of adolescent subject’s treatment

responsibility, Part 3: Report of parent/ caregiver's treatment responsibility. The ATR-Caregiver has the same 3 parts.

- Behavior Rating Inventory of Executive Function (BRIEF) is a validated measure designed to assess executive function in daily life. The *BRIEF2-P* (*Parent version*) is a 63-item validated measure that documents the parent's perception of their child's problem-solving and behavioral functioning. This form will be administered to parents of participants under18 years of age. The *BRIEF-A (Adult version)* is a 75-item validated, self-report measure for participants 18 or older. Both study forms take approximately 10-15 minutes to complete and measure different aspects of executive function, such as inhibition, self-monitoring, organization, planning, and emotional control. The BRIEF is scored against population normative data and reported as an overall summary score with subscales and two broad indexes (behavioral regulation and metacognition). Both versions of the BRIEF have high reliability, validity and clinical utility across diverse disease populations and age groups.

- Heart Transplant Knowledge Questionnaire (adapted for KT) is a 20-question survey used to assess the participants understanding of their medication, transplant and healthcare plan. The survey resembles a quiz, with each multiple choice and true/false question having only one correct answer.

- Knowledge of Spina Bifida (KOSB) is an 18-item survey assessed as a summary score.[57] Higher scores indicate greater knowledge.

- Self-Efficacy for Managing Chronic Disease 6-Item Scale is a Likert-scale survey that measures the following six domains of self-efficacy: (1) fatigue, (2) physical discomfort, (3) emotional distress, (4) symptoms or health problems, (5) health-related self-management tasks and (6) taking medicines.[58] Each item is answered on a 10-point Likert scale, with higher scores representing greater healthcare self-efficacy.

- Sharing of Spina Bifida Management Responsibilities – Child and – Parent (SOSBMR-C and -P) measure perceived responsibility for health-related tasks, asking who took responsibility, child, parent or equal, for 34 health-related tasks pertaining to SB.

- Spina Bifida Barriers and Cathing Barriers Measures are two barriers measures combined into one survey for ease of administration. The first, SB Barriers, was used in a prior study by Dr. Alexandra Psihogios, a member of the DCC study staff. This measure was adapted from a validated diabetes barriers scale and asks subjects about their perceived barriers to proper care. The Cathing Barriers Measure is not formally validated but showed content validity in a recent study.[59] The survey asks subjects to indicate the items that make cathing difficult and then to rank the top three items out of those indicated. To our knowledge, there are no validated measures that address perceived barriers to cathing for the SB population.

- Way to Health Exit Survey measures the efficacy of the Way to Health portal as a tool for the research and engagement of AYA with a kidney transplant of spina bifida in

their health care management. This measure was developed by the study research team; it asks about the participants' attitude towards the portal, the study and asks about the effectiveness of the portal.

# 6 STATISTICAL CONSIDERATIONS

## 6.1 Primary Endpoint

The primary endpoint for this pilot clinical trial is to compare the efficacy of two 6-month mhealth-based interventions to promote treatment adherence among AYA with KT or SB.

The **independent variable** in the analyses for Aim 1 is *exposure to feedback + incentive* (intervention, Arm 2). The **dependent variable**, or primary outcome measure, is: change in the *proportion of weeks with adherence behavior ≥ 85% expected between baseline (run-in period) and intervention period*. Weekly adherence proportions will be calculated by observing the number of non-missed/late treatment episodes over the total number of episodes in that week.

The outcome will then be the proportion of weeks with treatment adherence ≥ 85%. Participants who do not submit the correct number of pictures within the prescribed window of their expected time due for treatment will be counted as nonadherent for that episode of med taking/cathing. Over the study period, changes in weekly timing adherence will be assessed as a repeated measure over time. In secondary analysis, we will examine variability in inter-dose intervals (based on time-stamping of photos) to account for doses that are taken beyond the time window.

## 6.2 Secondary Endpoints

The secondary endpoint for SB subjects is change in bladder wall compliance as assessed by urodynamic studies (UDS) at study entry and study end.

We expect that SB subjects who perform CIC as prescribed will experience either no change or improvement in bladder compliance compared with those who do not improve their CIC adherence behavior. We expect nonadherence with CIC to result in either no change or worsening from baseline.

For KT subjects, the secondary endpoint is change in CV of immunosuppressive drug levels (tacrolimus or sirolimus) between the baseline (run-in) and intervention period. CV of immunosuppressive drug levels will be compared with the real-time adherence measures of mobile phone camera reporting.

Other important outcomes examined in exploratory analysis include rejection, de novo donor specific antibody accumulation, graft loss and death.

## 6.3 Tertiary Endpoints

The tertiary endpoint is to identify psychosocial correlates of adherence changes in AYA with KT and SB. We hypothesize that improved treatment adherence from baseline to intervention

end will be mediated by increases in self-efficacy and healthcare responsibility and declines in perceived barriers, but will not be related to knowledge gained. We also hypothesize that we will observe greater changes in self-efficacy in Arm 2 vs. Arm 1 because of the specifically targeted text messages that emphasize people's progress and ability to perform difficult behavior. For this Aim, all participants will complete the baseline survey measures of self-efficacy, healthcare responsibility, perceived barriers and knowledge again at the end of the 6-month intervention via WTH. The **independent variables** in the analyses for Aim 3 are: 1) change in self-efficacy score 2) change in healthcare responsibility score 3) change in perceived barriers and 4) change in knowledge score from baseline to end of intervention. The **dependent variable**, or primary outcome measure, is: change in the *proportion of weeks with adherence behavior performance ≥ 85% prescribed/expected between baseline (run-in period) and intervention period*. A secondary analysis will examine usage of the educational modules viewed in the WTH portal. Usage will be tracked as yes/no and time spent. We hypothesize that increased usage will associate with increased knowledge but will have no effect on increased treatment adherence. Prior research supports the hypothesis that increased knowledge is not sufficient to promote positive health behavior.

### 6.4 Quaternary Endpoints

The quaternary objective is to evaluate differences in comorbidities and demographic data of lost to follow up participants to that of those who are complete the study intervention. We hypothesize participants with comorbid or more severe conditions may be less likely to complete or participate in the study.

### 6.5 Statistical Methods

Clinical and demographic variables will be compared with chi-square or two-sample t-tests for parametric and Fisher's exact or Wilcoxon rank-sum tests for non-parametric data. Treatment groups will be compared with similar analyses to confirm equity in randomization. We will compare change over time in % adherence between arms by fitting quasi-least squares (QLS) and generalized estimating equation (GEE) longitudinal models. The QLS/GEE models include a regression model for the primary outcome variable, in addition to a separate model for the correlation amongst the repeated measures on each subject. The AR (1) correlation structure is plausible because it forces a decline between measures with increasing separation in time; however, we will assess the sensitivity of results to choice of structure. In addition, the models will include treatment group and a time by treatment group interaction. If the interaction term differs significantly from zero, this will indicate that the change over time differs significantly between treatment groups. All analyses will follow the intention-to-treat principle. We will analyze the results for each disease group (SB, KT) separately, although the overall analytical models are the same.

Analysis for Aim 1 and Aim 2 will utilize GEE/QLS models to compare the change over time in the outcome between arms.

For Aim 3, Pearson's or Spearman's Correlations will be calculated to observe the association between outcome and each independent variable.

The statistical analysis will follow the intention-to-treat principle.

## 6.6 Sample Size and Power

The disease groups (KT or SB) will be analyzed separately in the primary analysis. We assume 180 KT and 180 SB recipients will complete the study, allowing for 10% drop-outs. With 90 participants per arm per disease group, setting alpha at 0.05, we will have >90% power to detect a medium effect size of 0.5 in timing change in proportion of timing adherence, using a two group t-test (based on TAKE-IT). Based on preliminary data from TAKE IT and published studies, it is reasonable to expect an average of 8% improvement in timing adherence when a behavioral economics model with financial incentives is applied.[53,57,104] An effect size of 0.50 would be observed if the difference in average improvement was 8% between groups, while the standard deviation of post minus pre improvement was 16. With 90 subjects per arm, the detectable effect size is also 0.50 for Aim 2. For Aim 3, a 0.050 two-sided Fisher's z test of the null hypothesis that the Pearson correlation coefficient is 0 will have 82% power to detect a correlation of 0.300 when the sample size is 90.

| Table 3. Anticipated Participant Enrollment | | | | |
|---|---|---|---|---|
| | Year 1 | Year2 | Year 3 | Year 4 * |
| Expected Participant Recruitment (Cohort 1 and 2) | 100 | 100 | 100 | 100 |
| Expected Parent Recruitment (Cohort 3) | 200 | 200 | 200 | 200 |
| Anticipated drop-outs (10%) | 30 | 30 | 30 | 30 |
| Anticipated cumulative n by end of study year | 270 | 540 | 810 | 1080 |

# 7 SAFETY MANAGEMENT

## 7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

## 7.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review. The Data Safety Management Board (DSMB) will review all adverse events.

This study supports and encourages bi-directional messaging. Because of this capability, study participants may reveal sensitive and serious thoughts or feelings, such as the desire to kill oneself, the occurrence of a serious medical incident requiring immediate medical attention

and other possibilities. While we expect events like this to be rare, we have implemented the following protocol to ensure these events are handled efficiently and effectively.

1. Study personnel will review participant-derived messages daily.
2. If a participant reaches out without the portal prompting him/her, an incident report is generated and sent to the site's research coordinator and the team project managers (DCC personnel).
3. Relying site coordinators are responsible for monitoring and addressing their site's incident reports and messages between normal working hours (0800-1700) Mondays through Fridays. The DCC is responsible for monitoring and addressing any incident reports and messages at all other times outside of the window mentioned.
4. If the content of the message (whether sent when prompted, reviewed in step 1, or sent when not prompted) indicates a serious adverse event, the coordinator who discovered the message will first contact the DCC PI, Dr. Sandra Amaral.
5. Dr. Amaral will decide how to proceed. Options include, but are not limited to, contacting the local treatment team, the team psychologist or an emergency response team.
6. If the coordinator cannot reach Dr. Amaral, the coordinator will contact the DCC psychologist, Dr. Lisa Schwartz.

A list of emergency contacts, including national hotlines for suicide prevention, child abuse support and more, is available to all study team members, and is attached to the eIRB application in section 12. Study personnel are instructed to have a low-threshold for contacting emergency response teams.

### 7.3 Incidental Findings

In rare cases, during the course of study procedures a participant may be found to demonstrate clinically significant incidental findings, such as signs of depression or domestic abuse. Members of the study team may consult with the psychologist or appropriate clinician to determine whether such a finding has enough health importance to the research participant to mandate or permit disclosure. At the study team's discretion, a qualified investigator or facilitator will inform the participant and/or the participant's family of the incidental finding at the next study visit. If the incidental finding is discovered at the last visit, every effort will be made to contact the participant by phone. The participant and/or the participant's family will be referred to an appropriate clinician or resource for follow-up when deemed necessary by the study team.

## 8 STUDY ADMINISTRATION

### 8.1 Treatment Assignment Methods

#### 8.1.1 Randomization

Subjects will be randomized to either Arm 1 or Arm 2, stratified by disease group (KT or SB) and age category (12-17 vs. 18-24) via user written code in Stata 14.0. The code will utilize a block randomization scheme that, within each disease/age group stratum stratification, first randomly orders blocks of size 2 and 4 then randomly orders subjects within blocks.

### 8.1.2 Blinding

Due to the nature of the study, it is not possible to blind subjects to their treatment assignment once they are assigned. Lead investigators at each site will be blinded to which Arm their participants are in. The research staff must know which participants are in which Arm in order to appropriately manage each participant.

## 8.2 Data Collection and Management

Each study subject will be assigned a study ID at the time of enrollment, which will serve as the means of protecting personal health information during data transfers and storage.

EPIC medical record will be entered into REDCap and study questionnaire data will be entered into the WTH platform. Coded electronic adherence data (i.e. picture messages) will be downloaded from the web-based mobile messaging service, Twilio, directly to the WTH Platform via secure data transfer. An additional data transfer will be used to extract a coded analytic data set to the CHOP server for analysis.

Way to Health Platform:

All personal information that the participant is asked to provide will be collected via WTH. WTH collects subjects' names, dates of birth, addresses, email addresses, and phone numbers. They also request the name and phone number of an alternate contact. To assure that participant confidentiality is preserved, individual identifiers are stored in a single password protected system that is accessible only to study research, analysis and IT staff. An investigator or statistician who logs in will be able to access only coded data. The WTH administrative group and research coordinators responsible for contacting participants for follow-up study visits or responding to questions about the study are able to view participant names and contact information.

The WTH web development team and Project Director currently have administrative access to PHI. All of these personnel will have completed Human Subjects Protection and HIPAA privacy training. The system automatically generates logs of all data queries which can be reviewed by research staff to ensure that no unauthorized persons have gained access to identifiable information. This system is hosted on site at The University of Pennsylvania (UPenn) and is protected by a secure firewall and several layers of operational security. Once a participant has been entered into this system, they are given a unique study identification number (ID). Any datasets and computer files that leave the firewall are stripped of all identifiers and individuals are referred to by their study ID. The study ID is also used on all analytical files.

The Penn Medicine Academic Computing Services (PMACS) is the hub for the hardware and database infrastructure that supports the project and the WTH web portal is built on this infrastructure. The data collected for WTH based studies is stored in My Structured Query Language databases on a PMACS-operated blade server environment devoted specifically to WTH. The data center is housed in Information Systems and Computing at 3401 Walnut Street. All data are stored in a single relational database, allowing researchers to correct mistakes. Every Structured Query Language (SQL) transaction, including accessing and changing data, is logged for auditing purposes. Data are entered into the database through

several different mechanisms. Participants enter their own personal information and respond to surveys through a PHP-based web interface. Researchers have a separate interface that allows them to manually enter data if needed. Data from biometric/monitoring devices are uploaded automatically, this includes data from mobile phones such as picture or text messaging. Datasets are blinded of all personally identifiable information when exported for analysis. The web application automatically removes all identifiers when a researcher requests an analytic dataset. The only people with access to identifiable participant information are pre-specified Research Coordinators responsible for contacting participants for follow-up. Personal information and research data will be stored in separate SQL tables and will be linked by a computer-generated ID number. Additionally, any information that leaves this system to communicate with third party data sources (biometrics devices, survey software, etc.) is stripped of any identifiers and transmitted in encrypted format. The same unique study ID is used to link these outside data to the participants.

The WTH Research Data Center staff is responsible for preventing unauthorized access to the trial participant tracking system database. The secure servers are located in a specially designed, highly secured facility at UPenn with dedicated uninterrupted power supply and strictly limited access. The study will utilize a client-server deployed Data Management System rather than a 'Store and Forward' database configuration, obviating research site database security concerns. Confidential participant information will be entered into the database. Thereafter, confidential information will be made available to authorized users only as specifically needed. No one can gain access to an individual SQL database table unless explicitly granted a user ID, password, and specific access. Even those with user names and passwords cannot gain access to the tables that contain the identifying participant information.

No results will be reported in a personally identifiable manner. All tracking system data will be password-protected with several levels of protection. The first will allow access to the operating system of the computer. The second will allow access to the basic menus of the integrated system; within certain menu options, such as database browsing, a third password will be required. WTH's team's prior research employing similar precautions has demonstrated that these techniques are very successful in assuring the protection of subjects.

The same procedure used for the analysis of automated data sources to ensure protection of participant information will be used for the survey data, in that subject identifiers will be used only for linkage purposes or to contact subjects. The study identification number, and not other identifying information, will be used on all data collection instruments.

Each investigator and staff member involved in the proposed study will sign and adhere to a Standard Operating Procedure for managing participant data through the WTH platform and has participated in required IRB/HIPAA compliance training. We will also continue to make use of password protection programs for all computerized records. In no instances will identifying information be publicly disclosed. Prior to conducting any analyses, all identifiers (e.g., names, medical record numbers, birth dates, etc.) will be removed. Results from this part of the investigation will be reported in aggregate.

1) Questionnaire Data:

This study will use the online survey tool Qualtrics to collect answers to survey questions from participants. The DCC research staff will build the surveys in Qualtrics and connect them to the WTH platform. Then participants will enter survey answers directly on their personal, password-protected WTH dashboard. Study staff members will review the survey content to ensure that no questions in any of the surveys ask for participant identifiers. To ensure no participant identifiable data is stored by Qualtrics, randomly generated 64 bit identifiers are used to link responses in Qualtrics to study events in the system. No PHI will ever be stored by this application in Qualtrics.

2) Electronic Adherence Data:

Following enrollment and completion of the participant's WTH profile, a research coordinator will help connect the participant's mobile device to the study's Twilio account. Twilio is a third party provider that supplies a unique mobile number with bidirectional, automatable SMS and picture messaging capabilities. If the participants do not have a phone with picture-taking capabilities, researchers will provide one. Data from Twilio will be uploaded automatically to the WTH platform. Once uploaded to WTH, the cellular transmission will have no participant-identifying information and after it is received in the platform, the content will be deleted from the Twilio servers. No IP addresses are collected during this information transfer. The coded daily adherence data will then be available to the study team on the secure, password-protected WTH platform.

The WTH portal applies security and privacy requirements generated by the HIPAA Security Rule and subsequently the HITECH requirements. Currently, the data is encrypted at rest and in motion in accordance with these laws and is certified by FDA.

3) EPIC Medical Record Data:

Study staff will extract relevant data (see section 5.1.1 Medical Record Review) from EPIC into REDCap via individual chart review. Individual subject data will be labeled with the subject's study ID upon population of REDCap for subsequent storage and data analysis.

Medical Record Review data will be managed and stored using the research-focused electronic web-based data capture system REDCap.

- Data listed in section 5.1.1 will be entered directly into REDCap. For exact data, please see the attached Medical Record Review survey (section 12.02 of our application)
- Research staff from relying sites will be on-boarded as external collaborators under the umbrella of Data Access Groups. These coordinators will only have access to their site's participant data. Research staff from the DCC will have access to all sites' data.
- Research staff at all sites will be required to obtain a Medical Authorization form to release/obtain patient information from the local institution to obtain medical record data of participant's transitioning to another institution for medical care during the study period. Method of receiving medical records data for participant's that consent to release of information will be determined by the institution's policy for sharing data.

- The following de-identification options will be used, when necessary, when exporting data for analysis: removing known identifier fields, hashing of record names, removing invalidated Text fields, Notes fields, or date fields and date shifting.

Data backup is performed nightly via a dedicated backup system. The backup environment is maintained by a dedicated staff using dedicated resources. Access to the backup environment is restricted to Research Information Systems staff.

Some medical record data will be stored in WTH as well. This data includes the participant's date of birth, address, email address and phone number.

Data Transfer Description

1.) Twilio to Way to Health platform: every day, deidentifed study adherence data will be downloaded from Twilio to the WTH platform. WTH code automates this transfer of data. Once data are received in the platform, the content will be deleted from the Twilio servers.

2.) Way to Health to Site Server: Coded data from the study visits, including initial survey, follow-up surveys, and adherence data will be converted to a CSV file and uploaded onto the CHOP server to a dedicated research folder on the study PI's virtual desktop (shared drive). No PHI will be involved in this transfer, only the subject's study ID.

All transferred and created files will be stored in a password-protected folder available only to study staff in the lead investigator's CHOP virtual desktop. All identifiers will be deleted following publication of the study results.

Study Recruitment Tracking File:

This password-protected Microsoft Excel file, saved on the PI's virtual desktop (shared drive) will include participant-identifying information necessary for registration, enrollment, and follow-up. Following enrollment, this document will be used to maintain a log of enrolled subjects. For families who are not enrolled, subject-identifying information will be destroyed. A non-identifiable list of subjects that were not enrolled will be retained for the purpose of calculating response rate.

Consent Forms:

Electronic copies of the consent forms will be stored in a password-protected folder on the PI's virtual desktop (shared drive). Participants will have access to the consent form throughout the study, via their WTH dashboard. If a participant turns 18 during the study, they will be re-consented by signing an electronic form through the WTH platform.

Anonymization:

Data will be extracted from the secure WTH platform for the purpose of data analysis. Any datasets and computer files that leave the WTH firewall will be stripped of all identifiers and individuals will be referred to by their study ID. The study ID will also be used on all analytical files.

## 8.3 Confidentiality

Access to the systems used for this project, including the WTH database, will be limited to staff who meet all relevant training requirements and are assigned to (or support) this project. Security procedures will follow the CHOP Information System Security Plan and in accordance with the National Institute of Standards and Technology Special Publication guidelines. All staff will have completed the Human Subjects Protection Training.

Electronic adherence monitoring data associated with the mobile application will be maintained by WTH, Inc. WTH has designed their database to comply with HIPAA regulations. Survey responses will also be stored on the WTH platform. The site is HIPAA compliant. The data are maintained on secure servers that are password-protected. Please see Section 8.2 for measures taken to assure confidentiality.

All results will be kept confidential and separate from the medical record. WTH will assign a study identification number to each subject, and all data will be coded under this number. The master list of subject names and identification numbers will be stored in a password protected excel file on a password protected computer. Only the study PI and study staff will have access to this excel file and password. Only the PI and assistant(s) directly involved in the research project will have access to the survey data.

No identifiable data will be used for future study without first obtaining IRB approval. The master list, linking PHI to study ID numbers, will be destroyed six years after data analysis is complete, in compliance with CHOP's data retention plan policy (A-3-9). Way to Health permissions will be adjusted so no PHI will be viewable by study staff..

## 8.4 Regulatory and Ethical Considerations

### 8.4.1 Data and Safety Monitoring Plan

A DSMB will be convened as needed, at least once annually, to ensure participant safety and study integrity. This board will consist of 4 faculty members, Drs. Nadia Downshen, Laura Mee, Jodie Smith and biostatistician Hauquin Zhoa, who are not directly involved in this research study. Specifically, at least one member will be a psychologist (Dr. Laura Mee). The DSMB will routinely assess issues of data quality, study fidelity and conduct, and adverse events. In the unlikely event of an adverse outcome associated with the study protocol, it will be immediately reported by investigators to the DSMB, the institutional IRBs and to the NIH, as appropriate. Any SAEs will be reported immediately to the principal investigator and the DSMB. At which time, a conference call will be set up for DSMB members to assess the event and make recommendations of action. The DSMB will also review interim and final data results to ensure no unanticipated harm (in terms of adherence behavior) occurred in either the intervention or comparison group. The DSMB will be apprised of study progress by email at a minimum of every 6 months.

### 8.4.2 Risk Assessment

There are no greater than minimal risks to subjects of this study. This is a randomized phase II clinical trial that will use participant clinical data obtained as part of routine medical care. Subjects in this study will not receive any additional medical procedures, such as biopsies or

lab work, beyond standard of care. Clinical data will be captured from the medical record database. This database is password protected and privilege for access is limited.

Subjects may decline to answer any question on any survey for any reason.

### 8.4.3 Potential Benefits of Trial Participation

Nonadherence, in both KT and SB populations, has grave consequences, including graft loss and dialysis for KT patients and kidney damage and failure for SB patients. Participants may benefit directly from this study by experiencing improved adherence and increased self-efficacy. Information gained from this study will help to identify whether this type of intervention is feasible and potentially effective. Thus, subjects enrolled in this study may provide indirect benefit to others by helping to set a path toward establishing evidence-based, effective interventions that impact longitudinal adolescent nonadherence and allograft/spina bifida outcomes.

### 8.4.4 Risk-Benefit Assessment

In relation to the potential benefit of this study, the risks of this study are small. Coordinators will closely supervise participants' adherence and parents/legal guardians will also be notified if adherence behavior becomes erratic to minimize the risk further.

## 8.5 Recruitment Strategy

Eligible subjects will be identified by screening the medical records of patients in the outpatient Nephrology, Urology and Spina Bifida clinics of the four participating sites. A member of the research team will ask the clinician's permission to approach eligible subjects in person or by telephone and offer information about the study. Where appropriate, subjects may be consented by phone by the study coordinator and be prompted to sign the electronic consent. Brochures with information about the study including inclusion criteria, study procedures and the contact information for study personnel will be available in clinic. Furthermore, the study staff may show an eligible patient the Welcome to U-REAACT video in clinic. Each site may use this video to post on media sources such as Nephrology and Urology departmental electronic newsletters, on their department website, or on their department social media page to teach patients about the study. When posting this link, the following description will be provided: U-REAACT uses text reminders, positive messaging and rewards to help keep teens with kidney transplants and spina bifida healthy. Contact [insert contact information here] to ask if you may be eligible for this research study!

## 8.6 Informed Consent/Assent and HIPAA Authorization

Those who choose to enroll in this study will be required to read a thorough description of the study objectives and methods. A member of the study staff will present the study consent form (electronically or hard copy) to each participant and parent/legal guardian and address any questions or concerns at the time of consent. Subjects less than 18 years of age will be required to provide verbal and written/electronic assent and also to obtain written/electronic parental consent. Subjects over 18 years of age will be required to provide written consent for

themselves. Subjects who consented or received parental consent may participate without their parent/legal guardians enrolling in the study. Parents/legal guardians of all subjects will be required to provide written consent for themselves to participate in this study. The IRB has waived consent and HIPAA authorization for the child's absent parent/legal guardian in the case that both parents/legal guardians are not present at time of enrollment. The waivers will occur for the purpose of collecting demographic information about the absent parent/legal guardian, such as income and education level. If both parents/legal guardians are present then both will be consented. Parents/legal guardians of eligible subjects may not participate if their child chose not to enroll in this study. It will be clearly stated, both verbally and within the text of the written/electronic consent, that participation in the study is voluntary and the decision to participate or decline participation will have no bearing on the medical care of the subject. Prospective subjects may take a paper consent form home to consider their interest in the study. No study procedures will take place prior to receiving a signed consent form. If the participant turns 18 years of age during the study, the subject will be prompted to re-consent by the Way to Health portal on or immediately after his/her 18th birthday and a new consent will be available to the participant via a direct URL and via his/her personal portal dashboard. The study team will be notified via text or email to call the participant to discuss the consenting process again and answer any questions.

## 8.7 Payment to Subjects/Families

Participants with a kidney transplant or the spina bifida diagnosis will be administered a Greenfire ClinCard at the time of enrollment. All compensation to the participant will be done electronically and participants will be able to access their funds once their card is activated by the DCC. All payments and prizes will be given to the adolescent or young adult. Parents will not be compensated. In the paragraphs below, the term participant refers to the AYA.

Participants will receive a lump sum of $20 at the end of the 2-week run-in interval if they have sent at least one photo during this time. After the run-in period, all participants will be paid monthly dependent on their participation. Participants will receive a monthly text message, sent via WTH or the Greenphire website, prompting them to check their money earned on the WTH portal.

Participants randomized to Arm 1 will receive $2/week throughout the entirety of the 6-month intervention period and the 6-month follow-up period to encourage real-time adherence reporting. Pay is not contingent on meeting a target adherence score, but only on submitting at least one photo at time of treatment per week.

Participants randomized to Arm 2 will receive a larger incentive of $10/week if they perform their desired treatment behavior at least 85% of the time. During the follow-up period, Arm 2 participants will get $2 per week for reporting. They will be eligible to receive an additional $10 for meeting their adherence target of $\geq$ 85% over a 2 week period (as opposed to one week during the intervention period). The incentive will then become $10 every month (if the average monthly goal is met), and finally no incentive beyond the $2 per week for reporting.

Participants in both arms who complete surveys at baseline, post intervention and post follow-up within 5 days of administration will receive $20 (per survey set). Participants who complete surveys within 6 – 10 days of administration will receive $10 (per survey set). Participants

with partially complete surveys, will not be eligible to receive survey compensation for the data collection time point. The DCC study staff will monitor taking behaviors and reports generated by the WTH platform to discern the amount of money owed to the participants every month. The amount owed will then be uploaded to each participant's ClinCard. To ensure participants are still in possession of study payment cards, study staff will contact participants at time of payment before allocating funds to the cards.

Furthermore, after subjects are consented and enrolled, they may earn small tokens of appreciation during the study to thank them for their continued participation. These tokens will be valued at ≤ $10 per item and may include such items as cell phone/smart phone covers, ear buds or water bottles. Subjects only be informed about the potential to receive such tokens for the completion of baseline surveys. They will not be informed about the potential to receive such tokens for the completion of future surveys nor will any tokens be provided prior to the consent process so as to not coerce subjects in any way. Subjects can earn these tokens by accumulating prize points. Prize points are administered when participants complete their intervention and follow-up surveys in a timely manner. 20 points/survey are earned for completing a survey on the day it is administered. Prize points decrease by 5 points/survey per day uncompleted until the potential to earn points is zero. Participants can earn up to 220 points. These points are redeemable for the aforementioned tokens, with 100 points approximately equivalent to a $10 item.

If a participant chooses to withdraw from the study, they will receive a text through the Way to Health portal thanking them for their participation and asking them for their feedback with a link to the exit survey. They may earn a $10 payment to their ClinCard if they choose to complete this survey within five days, as to mimic the compensation they would have received for completing this survey at the end of the study. All participants will have the option to complete this survey; participants who complete the study may earn prize points for the exit survey, along with their other follow-up surveys.

## 9 INTENTION FOR PUBLICATION

The research staff intends to submit a minimum of two manuscripts for publication in peer-reviewed journals. Additionally, throughout the duration of the study, research staff will submit abstracts and posters to present at conferences hosted by organizations such as the American Society of Nephrology, the Eastern Society of Pediatric Research, the American Transplant Conference and more.

## 10 REFERENCES

1. O'Hara LK, Holmbeck GN. Executive functions and parenting behaviors in association with medical adherence and autonomy among youth with spina bifida. *J Pediatr Psychol.* 2013;38(6):675-687.
2. Annual Data Report of the US Organ Procurement and Transplantation Network. Preface. *Am J Transplant.* 2014;14 Suppl 1:5-7.
3. Levine MH, Reese PP, Wood A, et al. Inferior allograft outcomes in adolescent recipients of renal transplants from ideal deceased donors. *Ann Surg.* 2012;255(3):556-564.

4. Smith JM, Ho PL, McDonald RA. Renal transplant outcomes in adolescents: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant.* 2002;6(6):493-499.
5. Ettenger RB, Rosenthal JT, Marik JL, et al. Improved cadaveric renal transplant outcome in children. *Pediatr Nephrol.* 1991;5(1):137-142.
6. Berquist RK, Berquist WE, Esquivel CO, Cox KL, Wayman KI, Litt IF. Adolescent non-adherence: prevalence and consequences in liver transplant recipients. *Pediatr Transplant.* 2006;10(3):304-310.
7. Shaw RJ, Palmer L, Blasey C, Sarwal M. A typology of non-adherence in pediatric renal transplant recipients. *Pediatr Transplant.* 2003;7(6):489-493.
8. Jarzembowski T, John E, Panaro F, et al. Impact of non-compliance on outcome after pediatric kidney transplantation: an analysis in racial subgroups. *Pediatr Transplant.* 2004;8(4):367-371.
9. Chisholm-Burns MA, Kwong WJ, Mulloy LL, Spivey CA. Nonmodifiable characteristics associated with nonadherence to immunosuppressant therapy in renal transplant recipients. *Am J Health Syst Pharm.* 2008;65(13):1242-1247.
10. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2012;12(5):1157-1167.
11. Gralla J, Tong S, Wiseman AC. The impact of human leukocyte antigen mismatching on sensitization rates and subsequent retransplantation after first graft failure in pediatric renal transplant recipients. *Transplantation.* 2013;95(10):1218-1224.
12. Foster BJ, Dahhou M, Zhang X, Platt RW, Smith JM, Hanley JA. Impact of HLA mismatch at first kidney transplant on lifetime with graft function in young recipients. *Am J Transplant.* 2014;14(4):876-885.
13. Shin M, Besser LM, Siffel C, et al. Prevalence of spina bifida among children and adolescents in 10 regions in the United States. *Pediatrics.* 2010;126(2):274-279.
14. Lee NG, Gomez P, Uberoi V, et al. In utero closure of myelomeningocele does not improve lower urinary tract function. *J Urol.* 2012;188(4 Suppl):1567-1571.
15. Panicker JN, Fowler CJ, Kessler TM. Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. *Lancet Neurol.* 2015;14(7):720-732.
16. Centers for Disease Control and Prevention: Spina Bifida: Research and Tracking. 2015; http://www.cdc.gov/ncbddd/spinabifida/research.html. Accessed October 30, 2015.
17. Psihogios AM, Holmbeck GN. Discrepancies in mother and child perceptions of spina bifida medical responsibilities during the transition to adolescence: associations with family conflict and medical adherence. *J Pediatr Psychol.* 2013;38(8):859-870.
18. Parmanto B, Pramana G, Yu DX, Fairman AD, Dicianno BE, McCue MP. iMHere: A Novel mHealth System for Supporting Self-Care in Management of Complex and Chronic Conditions. *JMIR Mhealth Uhealth.* 2013;1(2):e10.

19. Snow-Lisy DC, Yerkes EB, Cheng EY. Update on Urological Management of Spina Bifida from Prenatal Diagnosis to Adulthood. *J Urol.* 2015;194(2):288-296.
20. Armour BS, Ouyang L, Thibadeau J, Grosse SD, Campbell VA, Joseph D. Hospitalization for urinary tract infections and the quality of preventive health care received by people with spina bifida. *Disabil Health J.* 2009;2(3):145- 152.
21. Ramachandra P, Palazzi KL, Holmes NM, Chiang G. Children with spinal abnormalities have an increased health burden from upper tract urolithiasis. *Urology.* 2014;83(6):1378-1382.
22. Ouyang L, Bolen J, Valdez R, Joseph D, Baum MA, Thibadeau J. Characteristics and survival of patients with end stage renal disease and spina bifida in the United States renal data system. *J Urol.* 2015;193(2):558-564.
23. Fischer N, Church P, Lyons J, McPherson AC. A qualitative exploration of the experiences of children with spina bifida and their parents around incontinence and social participation. *Child Care Health Dev.* 2015.
24. Sabaté E, WHO Adherence to Long Term Therapies Project., Global Adherence Interdisciplinary Network., World Health Organization. Dept. of Management of Noncommunicable Diseases. *Adherence to long-term therapies: evidence for action.* Geneva: World Health Organization; 2003.
25. Guilfoyle SM, Goebel JW, Pai AL. Efficacy and flexibility impact perceived adherence barriers in pediatric kidney post-transplantation. *Fam Syst Health.* 2011;29(1):44-54.
26. Feinstein S, Keich R, Becker-Cohen R, Rinat C, Schwartz SB, Frishberg Y. Is noncompliance among adolescent renal transplant recipients inevitable? *Pediatrics.* 2005;115(4):969-973.
27. Stubberud J, Langenbahn D, Levine B, Stanghelle J, Schanke AK. Goal Management Training improves everyday executive functioning for persons with spina bifida: self-and informant reports six months post-training. *Neuropsychol Rehabil.* 2014;24(1):26-60.
28. Tucker CM, Fennell RS, Pedersen T, Higley BP, Wallack CE, Peterson S. Associations with medication adherence among ethnically different pediatric patients with renal transplants. *Pediatr Nephrol.* 2002;17(4):251-256.
29. Kinsman SL, Levey E, Ruffing V, Stone J, Warren L. Beyond multidisciplinary care: a new conceptual model for spina bifida services. *Eur J Pediatr Surg.* 2000;10 Suppl 1:35-38.
30. Simons LE, Blount RL. Identifying barriers to medication adherence in adolescent transplant recipients. *J Pediatr Psychol.* 2007;32(7):831-844.
31. Jamieson NJ, Hanson CS, Josephson MA, et al. Motivations, Challenges, and Attitudes to Self-management in Kidney Transplant Recipients: A Systematic Review of Qualitative Studies. *Am J Kidney Dis.* 2015.
32. Bloemen MA, Verschuren O, van Mechelen C, et al. Personal and environmental factors to consider when aiming to improve participation in physical activity in children with Spina Bifida: a qualitative study. *BMC Neurol.* 2015;15:11.
33. Delucchi A, Gutierrez H, Arrellano P, Slater C, Meneses M, Lopez I. Factors that influence nonadherence in immunosuppressant treatment in pediatric transplant recipients: a proposal for an educational strategy. *Transplant Proc.* 2008;40(9):3241-3243.

34. Shemesh E, Annunziato RA, Arnon R, Miloh T, Kerkar N. Adherence to medical recommendations and transition to adult services in pediatric transplant recipients. *Curr Opin Organ Transplant.* 2010;15(3):288-292.
35. Ingerski L, Perrazo L, Goebel J, Pai AL. Family strategies for achieving medication adherence in pediatric kidney transplantation. *Nurs Res.* 2011;60(3):190-196.
36. Wu YP, Aylward BS, Steele RG. Associations between internalizing symptoms and trajectories of medication adherence among pediatric renal and liver transplant recipients. *Journal of pediatric psychology.* 2010;35(9):1016-1027.
37. Volpp KG. The Counseling African Americans to Control Hypertension study and ways to enhance the next wave of behavioral interventions. *Circulation.* 2014;129(20):2002-2004.
*38.* Schafer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *American journal of Transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2008;8(3):616-626.
39. Shemesh E, Fine RN. Is calculating the standard deviation of tacrolimus blood levels the new gold standard for evaluating non-adherence to medications in transplant recipients? *Pediatr Transplant.* 2010;14(8):940-943.
40. Psihogios AM, Kolbuck V, Holmbeck GN. Condition Self-Management in Pediatric Spina Bifida: A Longitudinal Investigation of Medical Adherence, Responsibility-Sharing, and Independence Skills. *J Pediatr Psychol.* 2015;40(8):790-803.
41. Dowshen N, Kuhns LM, Gray C, Lee S, Garofalo R. Feasibility of interactive text message response (ITR) as a novel, real-time measure of adherence to antiretroviral therapy for HIV+ youth. *AIDS Behav.* 2013;17(6):2237-2243.
42. Miloh T, Annunziato R, Arnon R, et al. Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging. *Pediatrics.* 2009;124(5):e844-850.
43. Halpern SD, French B, Small DS, et al. Randomized trial of four financial-incentive programs for smoking cessation. *N Engl J Med.* 2015;372(22):2108-2117.
44. Kullgren JT, Troxel AB, Loewenstein G, et al. Individual- versus group-based financial incentives for weight loss: a randomized, controlled trial. *Ann Intern Med.* 2013;158(7):505-514.
45. Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. Financial incentive-based approaches for weight loss: a randomized trial. *JAMA.* 2008;300(22):2631-2637.
46. *Health Behavior and Health Education: Theory, Research, and Practice.* 4th ed. San Francisco, CA: Jossey-Bass.
47. List JA, Samek AS. The behavioralist as nutritionist: leveraging behavioral economics to improve child food choice and consumption. *J Health Econ.* 2015;39:135-146.
48. Loewenstein G, Price J., Volpp K. Habit formation in children: evidence from incentives for healthy eating. 2015. http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2497104. Accessed October 18, 2015.

49. Cannuscio CC, Dupuis R, Graves A, et al. A behavioral economics intervention to encourage epinephrine-carrying among food-allergic adults: a randomized controlled trial. *Ann Allergy Asthma Immunol.* 2015;115(3):234-240 e231.
50. Dowshen N, Kuhns LM, Johnson A, Holoyda BJ, Garofalo R. Improving adherence to antiretroviral therapy for youth living with HIV/AIDS: a pilot study using personalized, interactive, daily text message reminders. *J Med Internet Res.* 2012;14(2):e51.
51. Schwartz L DL, Butler E, Bonafide C, Dowshen N, Hobbie N, Kersun L, Pierce L, Szalda D, Li Y, Barakat L. A Text Messaging Intervention for Adolescents and Young Adults Recently Off Treatment for Cancer. Presentation at the Society of Pediatric Psychology Annual Conference, San Diego, CA. 2015.
52. American Society of Transplantation: Patient Information. http://www.myast.org/content/patient-information. Accessed October 31, 2015.
53. National Kidney Foundation, NKF Cares: Patient Information Center. https://www.kidney.org/patients. Accessed October 31, 2015.
54. UNOS. United Network for Organ Sharing: Transplant Living. http://www.transplantliving.org/pediatric/.
55. Centers for Disease Control and Prevention: Living with Spina Bifida. http://www.cdc.gov/ncbddd/spinabifida/living.html. Accessed October 31, 2015.
56. National Spina Bifida Association. Learn. http://spinabifidaassociation.org/. Accessed October 31, 2015.
57. Greenley RN, Coakley RM, Holmbeck GN, Jandasek B, Wills K. Condition-related knowledge among children with spina bifida: longitudinal changes and predictors. *J Pediatr Psychol.* 2006;31(8):828-839.
58. Ritter PL, Lorig K. The English and Spanish Self-Efficacy to Manage Chronic Disease Scale measures were validated using multiple studies. *J Clin Epidemiol.* 2014;67(11):1265-1273.
59. Lim SW, Lee HE, Davis M, Park K. Perceived Barriers and Difficulties of Intermittent Catheterization: In Korean Patients with Spinal Dysraphism and Their Parents. *Nuerourology and Urodynamics*. 2016:35:395-399.