Study Protocol

A Pilot Trial of UrApp, a Novel Mobile Application for Childhood Nephrotic Syndrome Management

Protocol Date: February 17, 2022

NCT04075656

A Pilot Trial of UrApp, a Novel Mobile Application for Childhood Nephrotic Syndrome

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MANUAL OF OPERATIONS

Version 4

17 FEBRUARY 2022

Contents

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SECTION 2: PROTOCOL

Background and Significance

Morbidity and burden of childhood nephrotic syndrome: *Idiopathic nephrotic syndrome (NS) is one of the most common chronic kidney diseases in children*, with a prevalence of approximately 16 cases per 100,000 children. NS is characterized by heavy urinary losses of protein leading to hypoalbuminemia, edema, and hyperlipidemia.[1] Children are treated with high-dose corticosteroids on presentation, and >80% respond to treatment with resolution of proteinuria and symptoms. However, 80-90% of the children initially sensitive to corticosteroids will experience disease relapse, with more than half relapsing frequently or becoming dependent on corticosteroids to maintain remission.[2-5] During a relapse, patients can suffer from anasarca, acute kidney injury, serious infections, or thromboembolic events. A cross-sectional analysis of the U.S. Kids' Inpatient Database from the Healthcare Cost and Utilization Project found that NS resulted in an estimated 48,700 inpatient days and charges totaling $259 million in 2006 and 2009. On average, a single NS hospitalization generated charges of $26,500. Furthermore,16% of the hospitalized patients had at least one serious complication, including thromboembolism, septicemia, peritonitis, pneumonia, and diabetes.[6]

Critical issues and barriers to optimal management: Management of children with NS entails long-term outpatient surveillance and treatment. Home care includes the important standard-of-care task of urine monitoring to follow the relapsing-remitting nature of the disease. Caregivers are trained to test the patient's urine routinely with test strips at home. These strips have small blocks of paper impregnated with various reagents that produce visible colorimetric reactions once in contact with urine, which can be interpreted by eye. One reagent block produces a semi-quantitative result for urine protein (**Figure 1**). New proteinuria signals disease relapse *before* the development of overt symptoms such as edema. Thus, patients are instructed to alert their providers to the occurrence of proteinuria in a timely manner so that corticosteroids can be initiated or adjusted to treat each relapse and prevent acute disease complications. It is also important for the patients to track urine protein for resolution so that corticosteroids can be stopped or reduced to minimize steroid toxicity.[7] For patients with significant corticosteroid side effects (e.g., hypertension, growth retardation, obesity), second-line agents are prescribed, which have additional side effects that require ongoing monitoring. Optimal NS disease management thus demands a high level of patient/caregiver vigilance and involvement to monitor the course of disease and communicate with providers.

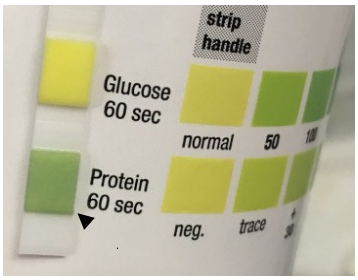


Figure 1. Urine test strip with protein reagent block (arrow).

Not unlike other chronic, relapsing-remitting pediatric disorders, self-management is difficult for NS patients and their caregivers. In a retrospective study of NS management and patient outcomes in the first 3 years following diagnosis at the Children's Healthcare of Atlanta (CHOA), we found that 39/87 (45%) NS patients ages 1 - 18 were documented by their physician to be nonadherent with urine monitoring and 43% were nonadherent with medications.[8] Similarly,

we found high levels of medication nonadherence in a survey study of 129 caregivers conducted through the multicenter Nephrotic Syndrome Study Network (NEPTUNE, NCT01209000): 71/129 (55%) respondents reported missing/skipping NS medications and 45/113 (40%) reported that their medication regimen was difficult to follow.[9] In a focus group and individual interview study, parents reported difficulty understanding the clinical meaning of urine protein results and knowing when to report and act on urine protein changes.[10] These issues in self-management may have a direct impact on disease outcome. A key finding that supports the importance of our work emerged from a prospective observational study of 64 pediatric patients enrolled in NEPTUNE. We found that self-reported *medication nonadherence during initial induction treatment was associated with delayed disease remission* (**Figure 2**; hazard ratio [HR] for reaching disease remission comparing adherent to nonadherent patients, 3.4; 95% confidence interval [CI], 1.2-10.6).[11] In this study, detailed adherence and disease status data was captured by mobile text messaging. We provided further support for the need to improve disease monitoring and management via an ancillary survey study of 72 pediatric nephrology providers conducted through the Cure Glomerulonephropathy study (CureGN). Fifty-seven percent reported that they "sometimes" (33%) or "often/always" (24%) do not learn about a disease relapse until patients have experienced disease complications, thereby missing a critical window when disease relapses may be treated to prevent complications. Furthermore, 46/72 (64%) providers reported that "sometimes" (53%) or "often" (11%) patients are kept on corticosteroids longer than intended because the provider does not find out in a timely manner that patients have reached disease remission (unpublished). There is a clear need for strategies to support self-management in childhood NS.

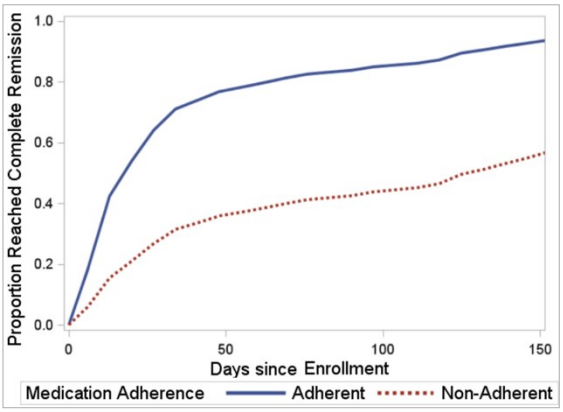


Figure 2. Time to remission among medication adherent vs. non-adherent pediatric patients with NS.

Rationale and significance of the proposed mobile health (mHealth) self-management support application (app): mHealth is a promising, rapidly growing field in disease management. Currently, 77% of U.S. adults own smartphones, and ownership is highest among younger adults (18-29 year-olds: 94%; 30-49 year-olds: 89%).[12] The ubiquitous presence of smartphones with advanced computing and communication capabilities, large memory, high quality cameras and other sensing capabilities are used to support home care for patients with chronic medical conditions and improve access to information.[13,14] Self-management support and clinical information systems are identified by the Chronic Care Model (MacColl Institute for Healthcare Innovation at Group Health Cooperative) as two key elements in effective care of chronic conditions. Viewed through this framework, mHealth apps can be effective interventions for chronic disease management.[15] In asthma, mHealth apps have been used to track day-to-day symptoms and provide individualized, timely reminders and education leading to improved clinical (e.g., symptoms, lung function) and patient-reported (e.g., adherence, self-efficacy, quality of life) outcomes.[16] Similarly, mHealth apps for diabetes self-management have

used smartphones to track home health data, including blood glucose, diet, and activity level. Data are used to provide personalized feedback such as insulin dosages and lifestyle coaching. While there are mixed results, a number of studies showed that app use resulted in improved HbA1c levels.[17]

In NS, there are numerous aspects of self-management that may be facilitated by a mobile app. First, the visual analysis of a urine test strip is subject to human error, including reading the wrong reagent block and erroneous assessments of color. This can be improved through using a smartphone's camera and computer to read and analyze test strip results. Second, caregivers must remember to check their child's urine, recall results, and understand what the results mean: the demands are taxing in that disease relapse is defined as urine protein ≥2+ for 3 consecutive days and remission is defined as negative/trace urine protein for 3 consecutive days.[2] Apps, with their inherent interactivity, can provide reminders for urine testing, capture the results, and analyze trends to detect disease relapse/remission. Apps can alert a caregiver to seek medical attention and directly transmit test results to providers. Lastly, apps can provide medication reminders for NS patients, who are on highly complex medication regimens. These mHealth capabilities support numerous components of effective management detailed by the Chronic Care Model: accurate assessment, action-planning, follow-up in self-management support, timely reminders for providers and patients, clinically relevant data tracking, and information sharing between providers and patients in clinical information system design.[18] In our unpublished survey study of 47 caregivers of children with NS, we found that 98% "agree/strongly agree" with a willingness to use an app to help with NS management. We also demonstrated in a NEPTUNE prospective study of 119 parents/patients assigned to mobile text-messaging for NS monitoring that mHealth technology was readily adopted by parents/patients (94%), and engagement with the technology was high (median response rate, 87%; interquartile range [IQR], 68-97%) over one year of follow-up (manuscript under review). Based on sound theoretical premise and evidence that caregivers would welcome mHealth apps for NS management, we built a novel app with features designed specifically to assist these families.

Theory-informed design of a novel interventional app for childhood NS self-management support and study plans: *UrApp* was iteratively developed by an expert panel of two pediatric nephrologists (the PI, Chia-shi Wang and Larry Greenbaum) and three research engineers with expertise in human-computer interaction at the Georgia Institute of Technology (GT). The formative UrApp development was funded by a research alliance between CHOA and GT. App features were devised by the clinicians to support elements of chronic care management according to the Chronic Care Model and tasks that are challenging for caregivers, as described above (**Table 1**).[18] The features were then iteratively refined by: 1) expert panel reviews of all user-app interface elements to eliminate anticipated use issues; 2) two rounds of simulated use testing with a total of 15 parents of children with NS and 5 adolescent patients where two observers noted all unforeseen use issues and participants were encouraged to provide simultaneous feedback via the "think-aloud" technique; and 3) semi-structured interviews soliciting users' overall impression and feedback for each app feature following simulated use testing. During the final round of simulated use testing, all 10 users were able to perform each app function without error, and all perceived UrApp to be helpful and indicated that they would

use UrApp (manuscript under review; **Figure 3**).

Table 1. Currently developed UrApp functions and the Chronic Care Model elements they support

Function	Specific Actions	Chronic Care Model Element
a) Urine test strip camera read	• Uses the iPhone camera to interpret the protein square on Roche Chemstrip 2GP® dipsticks • Users aim the camera at the test strip to perform a reading. Results are read within seconds as "normal (green)" for "negative/trace" findings, "moderate (yellow)" for "1+," and "high (red)" for "2+/3+"	• **Self-management support**: provides basic information; facilitates disease assessment; emphasizes patient's central role in care
b) Alerts for significant urine protein findings	• Generates alerts to the user for new disease relapse, newly achieved disease remission, or prolonged disease relapse > 2 weeks • Prompts user to send the result to their provider and call their provider	• **Self-management support**: provides basic information; facilitates disease assessment; emphasizes patient's central role in care • **Clinical information systems**: provide timely reminders for patients; summarizes data; shares information with patients
c) Transmission of urine protein results	• Generates an auto-populated e-mail with testing results. User indicates with one click that they agree with the transmission. • User can send results at any time through UrApp.	• **Clinical information systems**: identifies subpopulations for proactive care; facilitates individual patient care planning; shares information with providers to coordinate care • **Delivery system design**: plans interactions and follow-up individualized to disease severity
d) Urine protein documentation	• Results are color coded for an intuitive read: "normal (green)" for "negative/trace," "moderate (yellow)" for "1+," and "high (red)" for "2+/3+." • Displays urine protein results in a line graph as well as by calendar.	• **Self-management support**: provides basic information; facilitates disease assessment • **Clinical information systems**: summarizes data, shares information with patients
e) Education materials	• Provides documents and videos on: disease complications; importance of urine monitoring; interpretation of urine protein results; how to check urine at home; diet guidelines for children taking corticosteroids; and low sodium diet.	• **Self-management support**: provides basic information; emphasizes patient's central role in care; organizes resources to provide ongoing support • **Decision support**: shares information with patients to encourage their participation
f) Medication and urine testing reminders	• Option for pop-up reminders for each entered medication: daily, twice a day, or three times a day • Option for pop-up daily reminders for urine testing	• **Clinical information systems**: provides timely reminders for patients • **Self-management support**: provides strategies to increase medication and urine testing adherence

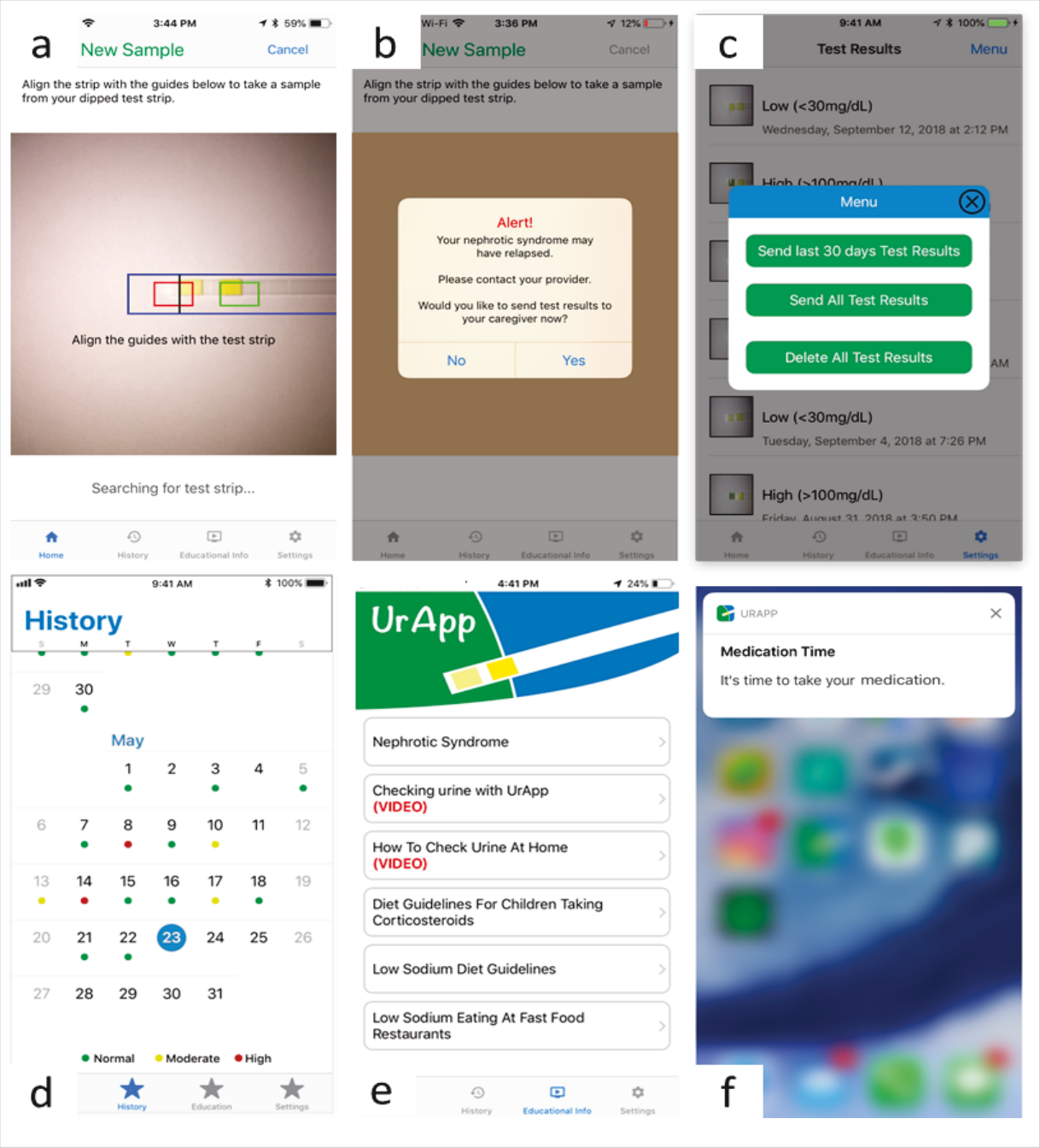


Figure 3. UrApp screenshots depicting: (a) urine test strip camera read, (b) alert for significant urine protein trend, (c) transmission of testing results to provider, (d) documentation of testing results in calendar format, (e) educational materials, (f) reminder for medication

Camera colorimetric assessment of urine protein test strip results: A key, technically innovative feature of UrApp is the camera colorimetric reading of urine test strips, developed and validated in Apple iPhone models 6S and 7 running iOS12. UrApp reads the Roche Chemstrip 2GP® (Indianapolis, IN) urine test strip, a widely available and validated urine dipstick.[19] After the app is activated, it instructs users to dip the test strip into the urine and then provides a count-down timer to ensure appropriate development time. Then, the user is prompted to aim the camera at the urine test strip (**Figure 3a**). Next, UrApp provides a read-out

of the result. Our manuscript describing the technical development of UrApp is currently under review. Validity testing: UrApp camera reads showed excellent agreement with standard urinalysis machine reads (Urisys 1100, Indianapolis, IN). Using 88 patient urine samples and three testers, exact agreement between UrApp and the urinalysis machine occurred in 253/262 (97%) tests. The weighted kappa value was 0.91 (95% CI, 0.85-0.97), indicating nearly perfect agreement between UrApp and the urinalysis machine read. Agreement between the three phone model versions was 100%. UrApp is the first mobile app to utilize the smartphone colorimetric analysis of urine test strips specifically for NS monitoring. With this innovative feature, patients and caregivers can easily perform home urine testing accurately. Furthermore, for the first time, clinicians/researchers have access to verified home urine testing results, allowing close monitoring and an unprecedented opportunity to study the relapsing-remitting disease course. UrApp is currently available for download in the Apple App Store.

Goals/Aims

Summary of work to date: We have 1) demonstrated the significance of self-management and the unmet need for a support tool in childhood NS; 2) established feasibility and interest in using mHealth interventions among NS patient caregivers; 3) soundly designed UrApp features that are grounded in theory with excellent preliminary user feedback and usability; and 4) established technical innovation and validity. *Our central hypothesis is that the use of a UrApp-based self-management support system will improve adherence with urine monitoring and medications.* We also predict that caregiver self-efficacy, patient and caregiver quality of life (QoL), and relapse detection will improve while hospitalization rates will decline.

In this proposal, we aim to rigorously test our hypotheses to gain sufficient preliminary data to advance the scalability and capacity of the intervention to impact outcomes in the real world. We plan to address crucial domains within the RE-AIM framework: *efficacy* (pilot trial to evaluate UrApp's impact on outcomes and stakeholder engagement to determine outcomes important to users), *adoption* (process evaluation to determine barriers/facilitators of app use and stakeholder involvement to refine the intervention design and create strategies to increase recruitment for a future trial), *implementation* (process evaluation of UrApp implementation and stakeholder involvement to redesign the intervention to ensure appropriate implementation), and *maintenance* (process evaluation to determine influences on use retention and user/stakeholder involvement to refine intervention design and plan a feasible clinical trial).[20] The "reach" domain is outside the scope of the pilot trial, though we have planned technical updates of UrApp to increase the number of iPhone versions it supports. Our specific aims are:

Aim 1. Evaluate the preliminary efficacy of UrApp among caregivers of children with nephrotic syndrome in a pilot trial. Participants will be randomized 1:1 to UrApp or SOC and followed for 1 year. Primary outcomes are medication and urine monitoring adherence. Secondary outcomes are self-efficacy, patient-reported quality of life, relapse detection, and hospitalizations.

Aim 2. In parallel with the pilot trial, perform a mixed-methods process evaluation of the

implementation of UrApp to determine the influences on its effectiveness.

Aim 2a. Evaluate UrApp engagement, use retention, and features used via user analytics and examine their relationships with UrApp efficacy with respect to primary and secondary outcomes.

Aim 2b. Explore user perceptions of UrApp features and barriers and facilitators of UrApp use via participant surveys and interviews.

Aim 3. Convene a committee of stakeholders of caregivers, clinicians, and mHealth engineers to collaboratively develop a user-centered UrApp enhanced nephrotic syndrome intervention program with the potential for wider implementation.

Aim 3a. Redesign as necessary the UrApp intervention to enhance UrApp use.

Aim 3b. Determine outcome measures most relevant to users and obtain user input on trial procedures to incorporate into the design of a future full-scale clinical trial.

Study Design

Overall design and organizational structure: 1:1 randomized trial of 1 year of UrApp use. The participants will be recruited from CHOA, Oregon Health and Science University (OHSU), University of Minnesota (UMn), and Medical University of South Carolina (MUSC). The trial will be followed by stakeholder engagement at CHOA to refine UrApp and plan a future large-scale trial.

CHOA will be led by the PI, Chia-shi Wang, Assistant Professor of Pediatrics. Dr. Wang will oversee all study administration; ensure compliance with applicable laws; lead a collaborative agreement on a uniform study protocol across all four sites; prepare all research documents including data collection forms/database and consent/assent forms; provide training to site investigators and coordinators on the study protocol and data entry; and ensure site adherence with the protocol and appropriate data entry.

OHSU will be led by site PI, Dr. Amira Al-Uzri, Professor of Pediatrics. Dr. Al-Uzri will ensure that the study is conducted in compliance with applicable laws and regulations and institutional policies; collaboratively work with other investigators to agree on a uniform study protocol; oversee the recruitment of study participants and adherence with the protocol; and update Dr. Wang on the study progress and potential issues.

UMn will be led by site PI, Dr. Michelle Rheault, Associate Professor of Pediatrics and Division Director of Pediatric Nephrology at UMn. Dr. Rheault will have the same responsibilities as other site PIs.

MUSC will by led by site PI, Dr. Katherine Twombley, Professor of Pediatrics and Chief of Pediatric Nephrology. Dr. Twombley will have the same responsibilities as other site PIs.

Site PIs at CHOA, OHSU, and UMn met and agreed on all procedural details, including standards for usual care, led by Dr. Wang. A Manual of Procedures was created. Each site will obtain local IRB approval (central IRB not required for a K23). Data entry and collection will be centralized via a REDCap database built by Dr. Wang.

The ECPI coordinator and Dr. Wang will provide data collection and entry training to the site PIs and coordinators.

Aim 1. Evaluate the preliminary efficacy of UrApp among caregivers of children with**nephrotic syndrome in a pilot trial.**

Participants and settings: 60 participants will be recruited from the nephrology clinics of CHOA,

OHSU, UMn, and MUSC. Sample size of 60 participants (randomized 1:1) will achieved 82% power to detect a 35% point difference in adherence with urine monitoring (primary outcome), with 20% drop-out. Sample size and power estimates are based on an adherence rate of 55% in the control group and 90% in the UrApp intervention group. These estimates are based on our single center experience with SOC[8] and our experience with text messaging for NS monitoring, where 94% of the participants continued to check urine and provide results via text messaging at the end of 1 year (manuscript under review). Power was calculated using a two-sided Z-test with pooled variance at 0.05 type I error rate using PASS v. 14.0.8 (Kaysville. UT). Our sample size exceeds the recommended minimum of 12 participants per arm for pilot studies.[20]

Inclusion criteria: Caregivers of patients ages 1-17 with steroid sensitive NS diagnosed within 42 days at time of enrollment; access to WIFI/internet; and proficiency with the English language. Exclusion criteria: end-stage kidney disease; renal transplantation; and clinical or histologic evidence of secondary NS (e.g., systemic lupus erythematosus).

Procedures: Participants will be enrolled and randomized 1:1 to UrApp or SOC treatment arms at the baseline visit between 2-6 weeks after diagnosis. Recruitment will continue for 2 years, and participant follow-up will be 1 year. Written caregiver consent and patient assent (verbal for children ages 6-10 and written for children ages 11 and above) will be obtained per local IRB guidance.

Randomization at each site will be carried out by an Emory biostatistician, Adrianna Westbrook, with no clinical involvement. She will generate the random allocation sequence using a pseudo- random-number generator with randomly permutated blocks stratified by study center.
Assignments will be placed in sealed, sequenced, opaque envelopes, which study coordinators will open at time of enrollment to assign participants to UrApp or SOC. Stratification by study center is appropriate to control for differing practices (e.g., differences in frequency of follow-up and patient education) that may affect outcomes (e.g., adherence to urine monitoring).

SOC arm participants will be provided a folder of educational material on NS, including general information on symptoms, treatments, and possible complications; healthy diet for children taking corticosteroids; and low sodium diet. Site research staff will demonstrate how to check urine for protein with test strips, and educate patients on the definitions of disease relapse and remission.[2] Urine test strips and urine protein logs will be provided to ensure that each participant can check their urine daily for protein. Participants will be instructed to check their urine daily for protein and call their provider within 1 business day for relapses and remissions. Since the majority of patients with NS are between 2-7 years of age,[21] participant education and materials provided will be targeted towards patient caregivers. Once in months 1-3 and 5-7, site research staff will contact the caregivers by telephone or in-person to follow-up on any questions regarding NS in general or urine monitoring. Any disease specific or treatment specific questions will be directed to the treating physician. Surveys will be administered by research staff in person at clinical visits at baseline, 6 months (+/- 1 month), and 12 months (+/- 1 month); caregivers will receive $20 per visit for their time.

UrApp treatment arm participants will follow the same procedures as described above for the SOC arm. For participants who do not own an iPhone, an iPhone will be loaned for the duration of the study. Caregivers/parents will download UrApp at the baseline visit. UrApp contains instructional videos to guide users. Participants will be instructed to test use the app, and all questions/difficulties using the app will be recorded by site research staff and resolved. The telephone number of the patient's provider will be entered into UrApp. Participants will be able to call their providers directly through UrApp. The email addresses of the local study staff and Emory's study staff will also be entered. UrApp

will automatically e-mail test results to the research staff when elected by the users. During the planned contacts in months 1-3 and 5-7, as described for the SOC arm, research staff will also inquire about any questions/technical issues with UrApp. These issues will be recorded and resolved. Participants will be asked by study staff, and reminded by the app, to call their providers and send urine testing results to the study staff whenever there is a relapse or remission. When the study staff receives alerts of a relapse/remission via UrApp, the information will be communicated to the treating physician within 1 business day. By the study staff receiving and monitoring urine testing results, we will be able to track participant behavior in notifying their physicians.

Measures/Materials

1) Baseline measures will be collected at the baseline visit between 2-6 weeks after NS diagnosis.

Demographic characteristics of the patient caregiver (UrApp user) and the patient will be collected from the medical chart and by participant questionnaire. Variables will include: caregiver age, gender, race/ethnicity, income level, and educational level; patient age, gender, and race/ethnicity. As one inclusion criteria for trial participation is ownership of an iPhone, examination of demographic variables will provide information on the representativeness of the cohort to the general NS population and the generalizability of study findings. Baseline self-efficacy and QoL will be assessed by surveys. Caregiver self-efficacy will be assessed by a survey adapted from the Self-Efficacy for Managing Chronic Disease 6-Item Scale (Stanford Patient Education Research Center). The survey will include 3 questions with a scale of 1/not at all confident to 10/totally confident. Patient/caregiver-reported QoL will be assessed by using the 23-item Patient-Reported Outcomes Measurement Information System - Pediatric Quality of Life Inventory (PedsQL). PedsQL was developed as part of the NIH Roadmap Initiative to create universal measures for patient-reported outcomes, and contains questions in the domains of social-peer, depression, anxiety, mobility, and function. The survey has been found to have validity and feasibility in children and adolescents with NS.[22] Caregivers and patients ages 5-17 will be surveyed with parent or patient forms, respectively.

2) Outcome measures will be collected at 6 and 12 months via caregiver surveys, medical chart review, and urine protein logs (UrApp data logs for the UrApp arm). We will perform 4 follow-up attempts within a 1-month timeframe to increase survey responses. Adherence to medications will be evaluated via caregiver survey with the validated 4 question Morisky, Green, and Levine (MGL) Adherence Scale.[23] We define adherence as a score of ≥3 on the MGL scale. Adherence with urine monitoring will be evaluated with a newly created questionnaire (**Figure 4**). In addition, UrApp data log (UrApp arm)

1) On average in the past month, how often did you check your child's urine for protein? *(Once a week, 2-4 times a week, or 5-7 times a week)*
2) In the past month, have you reduced how often you check your child's urine because he/she is in remission? *(Yes or No)*
3) In the past month, have you increased how often you check your child's urine because he/she is in relapse? *(Yes or No)*

Figure 4. Urine protein monitoring questionnaire.

and urine protein logs (SOC arm) will also be collected to obtain the frequency of monitoring. *A priori*, we define adherence with urine protein monitoring as checking, on average, at least 2 times a week in the month preceding the assessment. Self-efficacy and QoL surveys will be administered in the same way as during the baseline visit. Relapse detection: patient medical charts will be reviewed for occurrence and frequency of delayed relapse reporting; defined as a relapse not reported to the treating physician until clinical manifestations or complications have occurred and/or only discovered during planned or unplanned visits or hospitalizations. Hospitalizations: medical records will be reviewed for the primary reason for admission and NS disease complications: bacterial peritonitis, septicemia, shock, blood clot(s), acute kidney injury, and seizures from hyponatremia or hypertension.

Analysis will follow the intention-to-treat principle to preserve the integrity of the randomization. Primary outcomes, adherence with urine monitoring and medications, will be analyzed via Chi-square test to compare the proportions of adherent patients in the UrApp vs SOC arms at 6 and 12 months. Results will be presented as group proportions and difference in proportions with associated 95% CIs. In an adjusted analysis using a generalized linear mixed model, we will examine the changes over time by testing the treatment arm (UrApp vs. SOC) by time (6 and 12 months) interaction. Models will include site as a random effect and adjust for any baseline characteristic differences between groups (including sex as a variable). Self-efficacy and QoL measures will be analyzed using linear mixed models. Models will include the effect of treatment (UrApp vs. SOC), time (baseline, 6 and 12 months), and the treatment by time interaction. Study center will be included as a covariate and/or a random effect. Post-hoc pairwise comparisons will be used to compare specific points in follow-up (6 and 12 months) to baseline within and across groups. Results will be presented as differences in means with associated 95% CIs. Baseline characteristics will be included in the models as covariates in an adjusted analysis. Three-way interactions will be utilized to explore the role of demographic characteristics and their association with treatment response. While not adequately powered to conduct a moderator analysis, effect sizes will be calculated by subgroup and will inform a future, full-scale study. Delayed relapse diagnosis and hospitalizations will be compared between the treatment arms using Poisson regression under the framework of generalized linear mixed models or generalized estimating equations to account for correlated data collected from the same individuals. Baseline characteristics will be included in the models as co-variates. Analysis will be guided by Adrianna Westbrook, and carried out using SAS v.9.4 (Cary, N.C.).

Aim 2. In parallel with the pilot trial, perform a mixed-methods process evaluation of the implementation of UrApp to determine the influences on its effectiveness. Process evaluation examines the extent to which an intervention is implemented as intended and the influences on its effectiveness, and is increasingly recognized as integral to both the development and assessment of health promotional programs.[24] Our UrApp-based intervention program is novel in the childhood NS field; hence, we will perform process evaluation alongside the pilot RCT to increase the *rigor* of this formative process to design an effective self-management support tool. Aim 2 design is collaboratively developed by Dr. Wang and experts in behavioral and implementation sciences, Drs. Cam Escoffery and Rachel Patzer.

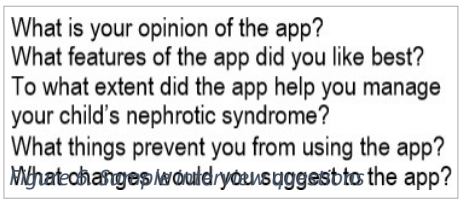
Aim 2a. Evaluate UrApp engagement, use retention, and features used via user analytics and

examine their relationships with UrApp efficacy with respect to primary and secondary outcomes. One of the main purposes of process evaluation is to determine the extent to which an intervention was delivered as intended. Key elements include: *fidelity* (delivery as planned) and *dose* (quantity of the intervention delivered and extent to which participants actively engaged with the materials including initial and continued use).[24,25] We operationalize these concepts as: UrApp engagement (frequency of use [*dose*]), retention (use over time [*dose*]), and app functions used and frequency of use (depth of use [*fidelity and dose*]).

Procedures and analysis: User behavior data are automatically captured by UrApp analytics and include information on: frequency of use, frequency of use over time, and specific app functions used and frequency. These measures will be downloaded at 6 and 12 months among participants in the UrApp arm (n=30). *A priori*, we define adequate engagement as accessing UrApp at least two times per week during the first 3 months, poor retention as a 50% decrease in weekly use over time, and adequate depth of use as transmission of data to providers for all episodes of disease relapse/remission when prompted. The relationship between user behavior and primary and secondary outcomes (detailed under Aim 1) will be assessed via Chi-square test/Fisher's exact test or t-tests or Wilcoxon rank-sum tests, as appropriate.

Aim 2b. Explore user perceptions of UrApp features and contextual barriers and facilitators of UrApp use via caregiver surveys and interviews. A second main purpose of process evaluation is to understand the contextual influences (i.e. barriers and facilitators) and user perceptions on an intervention's implementation and success.[24,25] To achieve this, we will survey the 30 participants randomized to the UrApp arm, followed by in-depth exploration through one-on-one interviews.

Procedures and Measures/Materials: Participant surveys on the general perceptions of mHealth apps will be obtained at baseline. A survey on the perceived usefulness, satisfaction, and ease of use of UrApp will be administered to caregivers at 6 and 12 months in the UrApp arm. Surveys items will be adapted from the USE Questionnaire, a survey designed specifically to measure user perceptions of mobile apps and other user support products.[26] Participants will receive $20 per survey. Interviews will be conducted with caregivers in the UrApp arm at 6 and 12 months via Zoom (for participants at UMn, OHSU, and MUSC). Interviews will follow a semi-structured guide created by Dr. Wang with input from Dr. Escoffery. Questions will target perceptions of the usefulness, satisfaction, and ease of use of UrApp and its specific features. Barriers and facilitators of UrApp use will be queried, as well as recommendations for changes to UrApp. The interviewers will lead with open-ended questions, with follow-up questions probing for understanding (**Figure 6**).
Caregivers will receive $50.



Analysis: Survey results will be tabulated and described for each study time-point. Baseline perceptions of mHealth apps and caregiver demographic characteristics will be examined for associations with UrApp perceptions at 6 and 12 months using Chi-square tests and two-sample t-tests or Wilcoxon rank-sum tests, as appropriate. Analysis of interviews will involve multiple steps to ensure data validity and reliability.[27] The interviews will be

transcribed verbatim. Transcripts will be analyzed using thematic analysis by identifying deductive and inductive themes. Transcripts will be coded by 2-3 independent coders using a qualitative data analysis software program (i.e., NVivo). A codebook will be developed for concise definition and to ensure consistency in code application. An initial list of deductive themes will be identified by Dr. Wang, given her clinical expertise. Inductive, data driven themes and concepts will be added as they emerge from the transcripts. Inter-coder agreement (2 coders) will be assessed prior to coding the whole dataset and discrepancies rectified. Data collection will stop once data saturation is reached (i.e., no new codes). Categories and sub-categories of themes from the qualitative interviews will be derived from the codes.

Aim 3. Convene a committee of stakeholders of caregivers, clinicians, and mHealth engineers to collaboratively develop a user-centered UrApp enhanced NS intervention program with the potential for wider implementation. Stakeholder engagement is an effective framework for ensuring that research is patient-centered, with results that have greater relevance and impact for the intended end users.[28] In this aim, we will integrate stakeholder involvement in the evaluation of the pilot trial results and plans for UrApp refinement and a future full-scale clinical trial. Our procedural approach incorporates elements of the Patient-Centered Outcomes Research Institute Engagement Rubric: *reciprocal relationships* (including partners as key personnel), *partnership* (fair compensation, reasonable and thoughtful requests for time, inclusiveness and respect), *co-learning* (researchers help patients and other stakeholders to understand the research process, patient-centeredness and stakeholder engagement incorporated), *transparency-honesty-trust* (inclusive decision making, information is readily shared, commitment to open and honest communication).[29] This will provide key multidisciplinary perspectives, including the voice of the patient caregiver, to increase the likelihood of a patient-responsive care management intervention and meaningful clinical trial. Our sub-aims are: Aim 3a. Redesign UrApp intervention to remove barriers and enhance UrApp use; and Aim 3b. Design a full-scale clinical trial (R01) to rigorously test UrApp with outcome measures most relevant to patient caregivers and feasible procedures to ensure recruitment and retention success.

Procedures: Stakeholder members will include: 1) Drs. Wang and Greenbaum; 2) GT research engineers with human-computer interaction expertise who developed UrApp and are intimately aware of technical possibilities/restrictions; 3) 5 patient caregivers in the UrApp arm who have completed 12 months follow-up. Participants in the UrApp arm at Emory will be approached for interest in joining the stakeholder committee during the pilot trial. Four face-to-face stakeholder meetings with a virtual (Zoom) conference option for members who cannot be present will be conducted. Meetings will be held every 1-3 months, with the first meeting starting at the end of pilot trial recruitment, when we anticipate having 6-months follow-up data on at least half of the trial participants. Caregiver members will be compensated $75 for each meeting, and food/drinks will be provided (fair compensation under *partnership*). Meeting 1 will focus on introducing members to each other and building relationships (*reciprocal relationships* and *trust*). We will outline the goals of the stakeholder committee to refine UrApp and plan a future trial (*co-learning*). A summary of the trial results to date on UrApp efficacy and process evaluation will be shared (*transparency*, *honesty*), and members will be invited to share their perspectives and interpretation of the trial results (*co-learning*). Meetings 2-4 will

include a review of updated trial results. Informed by the trial results, the committee will iteratively plan UrApp refinement (*transparency, co-learning,* and *reciprocal relationships*). Caregivers will provide input on outcomes most important to users. The investigators will use the feedback to iteratively develop measures/procedures to be reviewed at subsequent meetings (*co-learning, reciprocal relationships*). Caregivers will provide feedback on the protocols to improve recruitment and retention.

SECTION 3: TRIAL TIMELINE AND RESEARCH TASKS

SOC Arm

	Enrollment[1]	**Baseline (Time 0)**	**V1[2]**	**V2**	**V3**
Acceptable time-frame	2-6 weeks after NS diagnosis	2-6 weeks after NS diagnosis	1-3 months	5-7 months	11-13 months
Consent/Assent	√				
Randomization		√			
Education material (folder and video)		√			
Urine test strip (2 bottles) distribution (check expiration date)		√		√	
Instruct: check urine daily and call provider for relapse/remission		√	√	√	
Demographic survey		√			
Self-efficacy survey		√		√	√
QoL surveys (parent and child)		√		√	√
Screening for issues or adverse events			√	√	√
Medication adherence survey		√		√	√
Urine testing adherence survey		√		√	√
Schedule follow-up	√	√	√	√	
Stipend distribution[3]		√		√	√
Clinical information CRF[4]		√			
Hospitalizations and Relapses CRF[4]				√	√

Abbreviations: CRF, clinical reporting form; NS, nephrotic syndrome, V, visit

[1]Enrollment visit can be performed on the same day as the Baseline Visit

[2]May be performed over the telephone or in-person

[3]$20

[4]Completed by the research staff

UrApp Arm

	Enrollment[1]	**Baseline (Time 0)**	**V1[2]**	**V2**	**V3**
Acceptable time-frame	2-6 weeks after NS diagnosis	2-6 weeks after NS diagnosis	1-3 months	5-7 months	11-13 months
Consent/Assent	√				
Randomization		√			
Education material (folder and video)		√			
Urine test strip (2 bottles) distribution (check expiration date)		√		√	
Instruct: check urine daily and call provider for relapse/remission		√	√	√	
Download UrApp and enter ID, clinic contact number, and Emory e-mail address		√			
Demographic survey		√			
Self-efficacy survey		√		√	√
QoL surveys (parent and child)		√		√	√
Health app perception survey		√			
UrApp feedback survey				√	√
Screening for issues or adverse events			√	√	√
Medication adherence survey		√		√	√
Urine testing adherence survey		√		√	√
Interview[5]				√	√
Schedule follow-up	√	√	√	√	
Stipend distribution[3]		√		√	√
Clinical information CRF[4]		√			
Hospitalizations and Relapses CRF[4]				√	√
Approach for stakeholder committee (Emory site only)					√

Abbreviations: CRF, clinical reporting form; NS, nephrotic syndrome, V, visit

[1]Enrollment visit can be performed on the same day as the Baseline Visit

[2]May be performed over the telephone or in-person

[3]$20; $50 will be sent from Emory directly to the participants at 6 and 12m for completed interviews

[4]Completed by the research staff

[5]Will be performed via Zoom, conducted by the Emory staff. Can be performed in-person or via the phone for participants at the Emory site.

SECTION 4: DETAILED TRIAL PROCEDURES

PARTICIPANTS

1. Recruitment Target

60 participants will be recruited from the nephrology clinics of CHOA (Emory), OHSU, UMn, and MUSC between Sept. 2019 – March 2022. We will plan a recruit to replace up to 20%.

2. Screening

1. A systemic screening procedure at each site is crucial to meeting the recruitment target.
2. Recommended screening methods include:
    a. Screen the inpatient census every day Monday – Friday for patients newly diagnosed with nephrotic syndrome
    b. Screen outpatient clinic appointments once a week for patients with newly diagnosed nephrotic syndrome
    c. Discuss the study with division providers and once a month send out reminders for patient referrals to the study
3. As much as possible, approach potential participants in person during an admission or clinic visit to discuss the study and perform screening of the inclusion and exclusion criteria (Appendix A. Participant Screening Checklist).
4. A Screening and Enrollment Log needs to be completed on an ongoing basis and submitted to the Emory site every 6 months (Appendix B. Screening Log).

3. Inclusion Criteria

1. Caregivers of patients ages 1-17 years
2. Steroid sensitive NS diagnosed within 42 days at enrollment
    a. Clinical diagnosis with edema, nephrotic range proteinuria (urine protein to creatinine ratio >2 mg/mg, or ≥ 300 mg/dL or ≥ 3+ protein on urine dipstick), and hypoalbuminemia ≤ 2.5 g/dL
    b. Resolution of proteinuria (negative/trace protein on urine dipstick) within 4 weeks of corticosteroid treatment
3. Access to internet/WIFI access in the home
4. Caregiver proficiency with the English language

4. Exclusion Criteria

1. End-stage kidney disease
2. Renal transplantation
3. Clinical or histologic evidence of secondary NS (e.g. systemic lupus erythematosus)

5. Consent / Assent and Enrollment

1. Written caregiver consent, patient assent (if applicable) will be obtained at enrollment.
    a. Appendix C1: Consent
    b. Appendix C2: Assent

2. Enrollment visit may be combined with the Baseline Visit, both of which must take placed between 2-6 weeks of diagnosis.

Telephone/Virtual option:

1. Study can be introduced for either arm over the telephone or over a tablet with video conferencing.
2. The phone call can be conducted by research coordinators over the secure telemedicine solution, Zoom (https://Zoom/), so that research division's research phone number can be displayed instead of personal numbers of coordinators. An IRB approved telephone consent form should be used
3. Over the tablet, site teams will use Zoom video conferencing with candidate participants who are seen in clinic. The tablet will be set up by clinicians who are seeing the potential participants for a clinical indication. The telephone consent form will also be used.

BASELINE VISIT

Once consent / assent has been obtained, open one envelop to assign participants to either the UrApp or SOC arm.

SOC Arm

1. Provide the participants with a folder of educational material on nephrotic syndrome (Appendix D1-D9. Educational Material).
2. Play the video on "Why Check Urine Protein".
3. Confirm that the participants understands how to check urine for protein and the definitions for a new disease relapse and remission. Review Appendix D2 as needed to confirm understanding.
4. Instruct families to check urine daily and log results onto the Urine Protein Log (Appendix D9).
5. Instruct families to call their provider within 1 business day for relapses and remissions.
6. Hand out 2 bottles of urine test strips, check expiration date
7. Administer surveys (Appendix E)
    a. Demographics (Appendix E1)
    b. Self-Efficacy (Appendix E2)
    c. PedsQL Parent Report (Appendix E3)
        i. pick the appropriate patient age group: 2-4, 5-7, 8-12, 13-18
    d. PedsQL Child Self Report (Appendix E4)
        i. pick the appropriate patient age group: 5-7, 8-12, 13-18
    e. Medication-take Scale (Appendix E6)
    f. Urine-monitoring Scale (Appendix E7)
8. Schedule V1 (can be a phone call) and V2
9. Distribute stipend for $20

<u>After the study visit</u>:

10. Complete Clinical Information CRF (Appendix F)
11. Complete Baseline Visit Data Entry on the Redcap Link.

UrApp Arm

1. Provide the participants with a folder of educational material on nephrotic syndrome (Appendix D1-D9. Educational Material).
2. Play the video on "Why Check Urine Protein".
3. Confirm that the participants understands how to check urine for protein and the definitions for a new disease relapse and remission. Review Appendix D2 as needed to confirm understanding.
4. Instruct families to call their provider within 1 business day for relapses and remissions.
5. Hand out 2 bottles of urine test strips, check expiration date
6. For participants without iPhones, loan participants a study iPhone. Sign Appendix K. iPhone Return Agreement.
7. Download UrApp onto the participant iPhone, instruct participant to go through UrApp functions and watch video on "Checking Urine with UrApp" (automatically starts).
8. Enter Participant ID, physician contact number (local site clinic number), and Emory research team e-mail address (peds.neph@emory.edu) under UrApp "Settings".
9. Administer surveys (Appendix E)
    a. Demographics (Appendix E1)
    b. Self-Efficacy (Appendix E2)
    c. PedsQL Parent Report (Appendix E3)
        i. pick the appropriate patient age group: 2-4, 5-7, 8-12, 13-18
    d. PedsQL Child Self Report (Appendix E4)
        i. pick the appropriate patient age group: 5-7, 8-12, 13-18
    e. Health App Perceptions Survey (Appendix E5)
    f. Medication-take Scale (Appendix E6)
    g. Urine-monitoring Scale (Appendix E7)
10. Schedule V1 (can be a phone call) and V2
11. Distribute stipend for $20

<u>After the study visit</u>:

12. Complete Clinical Information CRF (Appendix F)

Complete Baseline Visit Data Entry on the Redcap Link Telephone/Virtual Visit option:

1. Conduct visit via Zoom video conferencing, administer surveys via RedCap link, and mail participants educational materials, iPhone (for participants without iPhones who are randomized to the UrApp Arm), urine test strip bottles, and stipend card:
    a. Research coordinators will set up a time to perform video conferencing with consented participants. A Zoom invite will be sent to the participants.
    b. During the video conferencing visit, the randomization folder will be opened by the site investigators and assignment explained to the participants.
    c. Study coordinator will play the education video for the participant over the video conferencing and check for understanding.
    d. Coordinator will instruct participants to check urine protein and notify providers for relapse/remission and then walk through UrApp download and use with the participants verbally following current procedures. A second Zoom video conference meeting will be

arranged for participants awaiting an iPhone to be mailed to them to review UrApp download and use again.

e. RedCap link surveys will then be sent via e-mail and participants will be reminded that upon completion of surveys, site staff will mail out stipend cards.
f. UrApp test strips (Albustix) and education folder will be mailed out immediately following the telephone baseline visit.
g. Remind participants with phone calls to complete surveys once a week for up to 4 reminders.

For participants who are seen in clinic, the video conferencing visit can be performed in clinic, with the clinician setting up the video conferencing. Participants can also complete the surveys on paper while in clinic, and receive in person the education folder, urine test strips, and stipend card from the clinician investigator.

Visit 1 (V1)

V1 can be conducted over the phone or in-person during a planned clinic visit.

SOC Arm

1. Follow Appendix G. Phone Interview Template for Nephrotic Syndrome Monitoring Issues
   a. Contact participant to see if they have any questions regarding the study or urine monitoring and screen for adverse events.
   b. Remind participants to check their urine daily and contact the provider for any new disease relapses or remissions or medical concerns.
   c. In case of adverse events (hospitalizations), see section below on "Adverse Event Reporting"
2. Confirm V2 date

UrApp Arm

1. Follow Appendix H. Phone Interview Template for Issues including UrApp Use
   a. Contact participant to see if they have any questions regarding the study, urine monitoring, or using UrApp and screen for adverse events.
   b. Remind participants to check their urine daily and contact the provider for any new disease relapses or remissions or medical concerns.
   c. In case of adverse events, see section below on "Adverse Event Reporting"
2. Confirm V2 date
3. Research Staff only - Contact the Emory Study Staff for any technical issues, and Emory will reach out to the participants directly to resolve the issues.

Visit 2 (V2)

SOC Arm

1. Follow Appendix G. Phone Interview Template for Nephrotic Syndrome Monitoring Issues
   a. Any questions regarding the study or urine monitoring and screen for adverse events.
   b. Remind participants to check their urine daily and contact the provider for any new disease relapses or remissions or medical concerns.

   c. In case of adverse events, see section below on "Adverse Event Reporting"
2. Hand out 2 bottles of urine test strips, check expiration date
3. Administer surveys (Appendix E)
   a. Self-Efficacy (Appendix E2)
   b. PedsQL Parent Report (Appendix E3)
      i. pick the appropriate patient age group: 2-4, 5-7, 8-12, 13-18
   c. PedsQL Child Self Report (Appendix E4)
      i. pick the appropriate patient age group: 5-7, 8-12, 13-18
   e. Medication Adherence (Appendix E6)
   f. Urine Testing Adherence (Appendix E7)
4. Schedule V3
5. Distribute stipend for $20

<u>After the study visit</u>:

6. Complete Hospitalizations and Relapses CRF (Appendix I)
7. Complete V2 Data Entry on the Redcap Link

UrApp Arm

1. Follow Appendix H. Phone Interview Template for Issues including UrApp Use
   a. Any questions regarding the study, urine monitoring, or using UrApp and screen for adverse events.
   b. Remind participants to check their urine daily and contact the provider for any new disease relapses or remissions or medical concerns.
   c. In case of adverse events, see section below on "Adverse Event Reporting"
2. Hand out 2 bottles of urine test strips, check expiration date
3. Administer surveys (Appendix E)
   a. Self-Efficacy (Appendix E2)
   b. PedsQL Parent Report (Appendix E3)
      i. pick the appropriate patient age group: 2-4, 5-7, 8-12, 13-18
   c. PedsQL Child Self Report (Appendix E4)
      i. pick the appropriate patient age group: 5-7, 8-12, 13-18
   d. Medication Adherence (Appendix E6)
   e. Urine Testing Adherence (Appendix E7)
   f. UrApp Feedback Survey (Appendix E8)
4. <u>OHSU,UMn, and MUSC only</u>: Obtain best times for a Zoom interview with the Emory Research Staff from the participant within the upcoming 2 weeks
   a. Discuss with the participant that the interview will likely take around 20 minutes and a $50 stipend will be mailed to them
5. Distribute stipend for $20
6. <u>Emory site only</u> – conduct participant interview (see below) and distribute stipend card for $50
7. Schedule V3 date

<u>After the study visit</u>:

8. Complete Hospitalizations and Relapses CRF (Appendix I)

9. OHSU,UMn, and MUSC Research Staff only – contact Emory Research Staff for the best times for Emory to conduct the Zoom interview with the participants
10. Complete V2 Data Entry on the Redcap Link

Telephone/Virtual Option:

1. Research coordinator will call participants over Zoom for iPhone and Android (https://www.doximity.com/clinicians/download/dialer), so that research division's research phone number can be displayed instead of personal numbers of coordinators.
    a. Coordinators will remind participants to check urine and call providers for disease relapses/remission.
    b. During this call, participants will also be reminded to complete surveys and that they will be receiving urine test strips and a study stipend.
    c. For participants in the UrApp Arm, a time will be set up to complete the interview.
2. RedCap link surveys will be sent via e-mail.
3. UrApp test strips will be mailed out.
4. Stipend (Clincard or check) will be dispersed after receipt of completed surveys
5. Remind participants with phone calls to complete surveys once a week for up to 4 reminders.

For participants who are seen in clinic for a standard of care visit, the instructions can be provided via video conferencing, with the clinician setting up the video conferencing. Participants can also complete the surveys on paper while in clinic, and receive in person the urine test strips and stipend card from the clinician investigator.

For participants in the UrApp Arm, a Zoom invite will be sent over e-mail for the interview. The Zoom interview will be conducted by audio or video conferencing depending on participant choice and availability of webcams. The audio portion of the conferencing will be recorded, as outlined in the original protocol and consent form. After the interview is completed, the participant's stipend (Clincard or check) will be dispersed.

Visit 3 (V3)

SOC Arm

1. Ask participants if their child has had any serious illnesses or hospitalizations.
    a. In case of adverse events, see section below on "Adverse Event Reporting"
2. Administer surveys (Appendix E)
    a. Self-Efficacy (Appendix E2)

   b. PedsQL Parent Report (Appendix E3)
      i. pick the appropriate patient age group: 2-4, 5-7, 8-12, 13-18
   c. PedsQL Child Self Report (Appendix E4)
      i. pick the appropriate patient age group: 5-7, 8-12, 13-18
   d. Medication Adherence (Appendix E6)
   e. Urine Testing Adherence (Appendix E7)
3. Distribute stipend for $20

After the study visit:

4. Complete Hospitalizations and Relapses CRF (Appendix I)
5. Complete V3 Data Entry on the Redcap Link

UrApp Arm

1. Ask participants if their child has had any serious illnesses or hospitalizations.
   a. In case of adverse events, see section below on "Adverse Event Reporting"
2. Administer surveys (Appendix E)
   a. Self-Efficacy (Appendix E2)
   b. PedsQL Parent Report (Appendix E3)
      i. pick the appropriate patient age group: 2-4, 5-7, 8-12, 13-18
   c. PedsQL Child Self Report (Appendix E4)
      i. pick the appropriate patient age group: 5-7, 8-12, 13-18
   d. Medication Adherence (Appendix E6)
   e. Urine Testing Adherence (Appendix E7)
   f. UrApp Feedback Survey (Appendix E8)
3. OHSU, UMn, MUSC only: Obtain best times for a Zoom interview with the Emory Research Staff from the participant within the upcoming 2 weeks
   a. Discuss with the participant that the interview will likely take around 20 minutes and a $50 stipend card will be mailed to them
4. Distribute stipend for $20
5. Emory site only – conduct participant interview (see below) and distribute stipend card for $50
6. Collect loaned iPhone.

After the study visit:

7. Complete Hospitalizations and Relapses CRF (Appendix I)
8. OHSU, UMn, and MUSC Research Staff only – contact Emory Research Staff for the best times for Emory to conduct the Zoom interview with the participants

Complete V3 Data Entry on the Redcap Link Telephone/Virtual Option:

1. Research coordinator will call participants over Zoom for iPhone and Android (https://www.doximity.com/clinicians/download/dialer), so that research division's research phone number can be displayed instead of personal numbers of coordinators.

   a. Coordinators will remind participants to check urine and call providers for disease relapses/remission.
   b. During this call, participants will also be reminded to complete surveys and that they will be receiving urine test strips and a study stipend.
   c. For participants in the UrApp Arm, a time will be set up to complete the interview.
2. RedCap link surveys will be sent via e-mail.
3. UrApp test strips will be mailed out.
4. Stipend (Clincard or check) will be dispersed after receipt of completed surveys.
5. Remind participants with phone calls to complete surveys once a week for up to 4 reminders.

For participants who are seen in clinic for a standard of care visit, the instructions can be provided via video conferencing, with the clinician setting up the video conferencing. Participants can also complete the surveys on paper while in clinic, and receive in person the urine test strips and stipend card from the clinician investigator.

For participants in the UrApp Arm, a Zoom invite will be sent over e-mail for the interview. The Zoom interview will be conducted by audio or video conferencing depending on participant choice and availability of webcams. The audio portion of the conferencing will be recorded, as outlined in the original protocol and consent form. After the interview is completed, the participant's stipend card (Clincard) will be refilled.

SECTION 5: HUMAN SUBJECTS SAFETY

Potential Risks/Discomforts and Confidentiality

The overall risks of the study are presumed to be minimal and primarily related to potential device-associated issues and loss of privacy/confidentiality.

Potential Device Issues: Several potential issues with the use of UrApp include: technical error in app interpretation of the urine test strip results; error in analyzing data trends and failure to alert users of new disease relapse/remission; and failed transmission of data to providers. These issues could result in delayed disease relapse and remission detection, leading to delayed treatment adjustment and potential development of disease complications (e.g. edema, acute kidney injury, blood clots) or treatment side effects (e.g. cushingoid symptoms with prolonged corticosteroid use).

Several safeguards are in place to minimize the risks and harms associated with the UrApp interventional device. With these safeguards and UrApp's design to provide patient reminders and management support, it is anticipated that the risks of delayed relapse/remission detection and potential development of complications/side effects to be equal, if not less, than standard of care.

1) A urine test strip protein reading is presented to the users by both a semi-quantitative read-out (normal, moderate, or high) along with the actual camera-captured image of the urine protein square. As the urine test strips provide a visible color change with the presence of protein, users have the ability to perform a visual interpretation of the urine test strip and should also be able to detect large discrepancies between the urine protein square color and the app interpretation. Furthermore, the images and the app readings are sent together when the results are transmitted to the research staff. Research staff should also be able to detect large discrepancies between the urine test strip results and the app reading. This is anticipated to be the most effective safeguard against technical failures of UrApp, thus minimizing the potential risks.

2) UrApp performs a light calibration with each urine test. If the light conditions are not optimal, the reading test strip read will not be performed. Users will not have the ability to override this safeguard. They are, however, able to enter the urine results by hand after visual interpretation. The visual interpretation will be noted as such in any data transmissions.

3) The data trends are stored in the app and presented to users graphically and by calendar format. After performing a urine test, users can see at a glance recent urine protein trends and detect errors in UrApp interpretations. Data transmitted to the research staff will also include all the reading results to detect any errors in analysis.

4) The study staff will discuss with participants that UrApp requires internet connection/WiFi to send results via e-mail to the study staff. UrApp also includes the same notice upon starting app use. Failure to send the results e-mail will be instantly alerted to user. The app will also prompt result transmission on a monthly basis at a minimum. The study staff will query results monthly and will contact participants if results have not been received.

5) Participants will be instructed to contact their providers by telephone for any new disease relapse/remission. The research team will also contact the patient's provider if app results are received indicating new disease relapse/remission within 1 business day.

6) The research staff will contact participants at 1-3 months and 4-6 months to screen for app use issues. Contact information will also be provided to users should they have any technical issues.

Privacy / confidentiality: Patient demographic and clinical information will be captured from questionnaires and medical charts with potential for breach of confidentiality. Survey data and interview data will solicit participant perceptions and self-reporting of adherence, self-efficacy, and quality of life, and may intrude on their privacy. Lastly, transmission of urine protein results from the app to the research staff may also result in a breach of confidentiality. Safeguards to minimize privacy intrusion and breach of confidentiality, as outlined below:

1) Study ID will be assigned with patient identifiers stored separately in password-protected computers accessible only to study staff.

2) Survey results, clinical data collected from the medical charts will be de-identified, stored in a data-encryption system (REDCap) in password-protected computers, and accessible only to study staff.

3) Surveys administered electronically will utilize the secure, encrypted REDCap system.

4) Interview recordings will be digitally stored along with transcripts in password-protected computers accessible only to study staff.

5) Interviews will be conducted in private conference rooms without windows.

6) Interviews will be conducted by trained research staff with field experience and understanding of respect for participant's privacy.

7) Participants using UrApp will be instructed to enter their Study ID as the identifier in the automatically generated e-mail containing the urine testing results, along with the sender's e-mail address. E-mail accounts set-up to receive data from UrApp will be created that are HIPAA-secure and accessible only to study staff.

8) The loaned iPhone for participants in the UrApp Arm without iPhones will be set up using an iTunes account created by the research team. The phone will be locked to the research team iTunes account so that participants cannot download other apps which may store personal information on the study iPhone. Thus, participant personal information will not be stored on the loaned iPhone. After the loaned phones are returned, the research staff will work with Emory IT department to ensure all participant information are deleted offthe loaned iPhones.

Benefits

Study participants are not expected to directly benefit from the proposed research plan during study participation. However, they may find the prototype of the app to be helpful for their disease management. Their participation is expected to create a novel, pragmatic, and effective tool for nephrotic syndrome management, which can be used by the participants themselves and others in the future.

Safety Monitoring

1. Emory will review app transmitted results every business day, and report any new relapse/remission to the treating physician within 1 business day.
2. At planned study contacts, study staff will screen for any technical difficulties with UrApp. The study staff will also contact participants in the SOC arm for any questions regarding nephrotic syndrome management tasks in general (e.g. how to check urinefor protein, what is the definition of a disease relapse) at the same planned study contacts. Any specific treatment concerns will be relayed to the treating physician.

Adverse Event Reporting

1. Screening for adverse events will be performed at each study contact, either by phone or in person.
2. A **serious adverse event** is defined as: death; life-threatening event; requires or prolongs hospitalization; results in disability significant, persistent, or permanent; pregnancy with a resultant birth defect; or causes cancer. The Adverse Event form (Appendix J) must been completed in RedCap within 2 business days, which will automatically generate notification to the PI and Emory study team, who will notify the DMC and Emory IRB within 2 business days after the study team became aware of the SAE. The PI will make an assessment of whether the event constitutes an unanticipated

problem posing risks to subjects or others. This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is an unanticipated problem, it will notify the appropriate regulatory agencies and institutional officials.

3. **Adverse events** that do not meet criteria for Serious Adverse Event will be reported using the Adverse Event Form (Appendix J) during the follow-up visit. Information regarding the diagnosis, date of occurrence, severity of the event, and therapy will be recorded. A determination of the relationship of the adverse event to the study participation will be made by the site PI. Should a relationship be found, results will be reported to the Emory PI and the DMC within 1 business week.

Data Monitoring Committee

An external **Data Monitoring Committee (DMC)** have been constituted prior to the randomization of the first patient. The DMC consists three individuals outside the Emory Division of Pediatric Nephrology with experience in clinical research. The DMC will perform the first safety review using a data cutoff 6 months after randomization of the first patient and every 6 months thereafter, unless otherwise requested by the Chair of the DMC. The DMC will also receive reports on a regular basis on all SAEs reported for this trial. Recruitment will not be interrupted unless otherwise requested by the Chair of the DMC. Results of the DMC review will be shared with the lead PI and all participating sites within 1 business week.

The study would be stopped if the DMC and the lead PI believe that there is a significant safety issue or that the interim analysis indicates that completing the study is not appropriate. Should a decision be made to stop the study, a report will be made to all participating sites within 2 business days.

SECTION 6: DATA MANAGEMENT AND MONITORING

REDCap, a secure data collection system that encrypts all data, will be used for data collection and management for all data collected from surveys and the medical charts. Interview transcripts will be stored digitally in a password protected computer. Interview analysis will use the software, NVivo, which provides data encryption. Access to both system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training. Site staff will receive training prior to receiving access to REDCap for data entry.

The PI, Chia-shi Wang, and the lead site coordinator will query data monthly and review entries for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via email. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data. After these actions have been completed and the data have been verified to be complete and accurate, the database will be declared locked and made available for data analysis.

There will be reports of enrollment by site completed every 6 months.

SECTION 7: REFERENCES

1. Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet.* 2003;362(9384):629-639.
2. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A Report of the International Study of Kidney Disease in Children. *Kidney Int.* 1981;20(6):765-771.
3. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *J Pediatr.* 1981;98(4):561-564.
4. Greenbaum LA, Benndorf R, Smoyer WE. Childhood nephrotic syndrome--current and future therapies. *Nat Rev Nephrol.* 2012;8(8):445-458.
5. Lombel RM, Hodson EM, Gipson DS, Kidney Disease: Improving Global Outcomes. Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. *Pediatr Nephrol.* 2013;28(3):409-414.
6. Gipson DS, Messer KL, Tran CL, et al. Inpatient health care utilization in the United States among children, adolescents, and young adults with nephrotic syndrome. *Am J Kidney Dis.* 2013;61(6):910-917.
7. Lombel RM, Gipson DS, Hodson EM, Kidney Disease: Improving Global O. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. *Pediatr Nephrol.* 2013;28(3):415-426.
8. Wang CS, Yan J, Palmer R, Bost J, Wolf MF, Greenbaum LA. Childhood Nephrotic Syndrome Management and Outcome: A Single Center Retrospective Analysis. *Int J Nephrol.* 2017;2017:2029583.
9. Wang C TJ, Srivastava T, Weidemann D, Greenbaum LA. Medication adherence and perceived difficulties in pediatric nephrotic syndrome. Paper presented at: ASN2017.
10. Beanlands H, Maione M, Poulton C, et al. Learning to live with nephrotic syndrome: experiences of adult patients and parents of children with nephrotic syndrome. *Nephrol Dial Transplant.* 2017;32(suppl_1):i98-i105.
11. Wang C TJ, Greenbaum LA, Srivastava T, Gibson K, Trachtman H, Herreshoff E, Gipson DS. Mobile text messaging for disease activity, stressors, and treatment adherence monitoring in pediatric nephrotic syndrome. Paper presented at: ASN2017.
12. Mobile Fact Sheet. 2018; http://www.pewinternet.org/fact-sheet/mobile/.
13. Klasnja P, Pratt W. Healthcare in the pocket: mapping the space of mobile-phone health interventions. *J Biomed Inform.* 2012;45(1):184-198.
14. Boulos MN, Wheeler S, Tavares C, Jones R. How smartphones are changing the face of mobile and participatory healthcare: an overview, with example from eCAALYX. *Biomed Eng Online.* 2011;10:24.
15. Slaper MR, Conkol K. mHealth tools for the pediatric patient-centered medical home. *Pediatr Ann.* 2014;43(2):e39-43.
16. Farzandipour M, Nabovati E, Sharif R, Arani MH, Anvari S. Patient Self-Management of Asthma Using Mobile Health Applications: A Systematic Review of the Functionalities and Effects. *Appl Clin Inform.* 2017;8(4):1068-1081.

17. Veazie S, Winchell K, Gilbert J, et al. In: *Mobile Applications for Self-Management of Diabetes.* Rockville (MD)2018.
18. Barr VJ, Robinson S, Marin-Link B, et al. The expanded Chronic Care Model: an integration of concepts and strategies from population health promotion and the Chronic Care Model. *Hosp Q.* 2003;7(1):73-82.
19. Chemstrip Urine Test Strips [package insert]. Roche Diagnostics Corporation., Indianapolis.IN. . 2010.
20. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* 1999;89(9):1322-1327.
21. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. *Kidney Int.* 1978;13(2):159-165.
22. Gipson DS, Selewski DT, Massengill SF, et al. Gaining the PROMIS perspective from children with nephrotic syndrome: a Midwest pediatric nephrology consortium study. *Health Qual Life Outcomes.* 2013;11:30.
23. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care.* 1986;24(1):67-74.
24. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ.* 2015;350:h1258.
25. Saunders RP, Evans MH, Joshi P. Developing a process-evaluation plan for assessing health promotion program implementation: a how-to guide. *Health Promot Pract.* 2005;6(2):134-147.
26. Lund A. Measuring usability with the USE questionnaire. *Usability Interface.* 2001;8(2):3-6.
27. Hennink M, Hutter, I., Bailey, A. *Qualitative Research Methods.* London: Sage; 2011.
28. Forsythe L, Heckert A, Margolis MK, Schrandt S, Frank L. Methods and impact of engagement in research, from theory to practice and back again: early findings from the Patient-Centered Outcomes Research Institute. *Qual Life Res.* 2018;27(1):17-31.
29. Sheridan S, Schrandt S, Forsythe L, Hilliard TS, Paez KA, Advisory Panel on Patient E. The PCORI Engagement Rubric: Promising Practices for Partnering in Research. *Ann Fam Med.* 2017;15(2):165-170.

SECTION 8: APPENDICES

A. Participant Screening Checklist

B. Screening and Enrollment Log

C. Consent and Assent Forms

C1. Consent for Group A – Incident Cohort

C2. Assent for Group A – Incident Cohort

C3. Consent for Group B – Prevalent Cohort (Emory site only)

C4. Assent for Group B – Prevalent Cohort (Emory site only)

D. Educational Material

D1. Nephrotic Syndrome

D2. How to Check Your Child's Urine for Protein at Home

D3. Diet Guidelines for Children Taking Corticosteroids

D4. Low Sodium Diet Guidelines

D5. Low Sodium Eating at Fast Food Restaurants

D6. Low Sodium for Children with Nephrotic Syndrome

D7. Pictures High Sodium Foods to Avoid

D8. Pictures of Quick, Lower Sodium Food Options

D9. Urine Protein Log

E. Surveys

E1. Demographics

E2. Self-Efficacy

E3. PedsQL Parent Report

E3a. PedsQL Parent Report for Toddlers (ages 2-4)

E3b. PedsQL Parent Report for Young Children (ages 5-7)

E3c. PedsQL Parent Report for Children (ages 8-12)

E3d. PedsQL Parent Report for Teenagers (ages 13-18)

E4. PedsQL Child Report

E4a. PedsQL Young Child Report (ages 5-7)

E4b. PedsQL Child Report (ages 8-12)

E4c. PedsQL Teen Report (ages 13-18)

E5. Health App Perception

E6. Medication Adherence

E7. Urine Testing Adherence

E8. UrApp Feedback Survey

F. Clinical Information CRF

G. Phone Interview Template for Issues

H. Phone Interview Template for Issues including UrApp Use
I. Hospitalizations and Relapses CRF
J. Adverse Event Form
K. iPhone Return Agreement