# Epilepsy Adherence in Children and Technology (eACT): Fostering Medication Adherence in Children With Epilepsy Using mHealth Technology

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**CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER**

**STUDY PROTOCOL**

**Study Title: EPILEPSY ADHERENCE IN CHILDREN AND TECHNOLOGY: A SEQUENTIAL, MULTIPLE ASSIGNMENT, RANDOMIZED TRIAL (SMART)**

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## 1. ABSTRACT

Non-adherence to antiepileptic drugs (AEDs) is a common problem (i.e., 58% of patients have some level of non-adherence) for young children with newly diagnosed epilepsy, with potentially devastating consequences. AED non-adherence is associated with a 3-fold increased risk of seizures, poor quality of life, inaccurate clinical decision-making, and higher health care utilization and costs. One of the primary barriers to adherence is forgetting, which may be particularly amenable to mHealth (mobile technology in healthcare) interventions. Despite the critical need to develop and implement interventions to improve adherence, there are few family-based interventions for young children with epilepsy and their families, with the exception of our work. Although highly promising, this intervention requires six in-person sessions, which can be impossible for families who lack routine access to tertiary specialty care due to time, financial, or transportation constraints. Thus, unmet medical and psychosocial needs of the underserved pediatric epilepsy population are perpetuated and compounded by limited access to this state of the art care. Our overall goal in this multisite study is to test an mHealth adherence intervention that is easily accessible using a stepped up care model based on individual needs. This stepped up care model will conserve patient, family, and provider time, costs and resources. We have completed the first phase of this work and incorporated the feedback we gathered from caregivers during focus groups and usability studies to develop the individualized adherence feedback reports, and all modules of the intervention (e.g., education and problem-solving web-based modules) to improve adherence.

The second phase of this study will consist of a 2-stage, sequential, multiple-assignment, randomized trial (SMART) to evaluate the effectiveness of mHealth intervention strategies for improving AED adherence in parents/legal guardians of young children with epilepsy. We plan to recruit a total of 600 participants across all collaborating study sites, with approximately 150 at each site. Enrolled caregivers will complete study questionnaires and be asked to start using electronic adherence monitors (e.g., pillbox or pill bottle) at the time of data enrollment during the baseline period. Only participants who demonstrate adherence $\leq$95% will be randomized to either the control group or treatment group in Stage 1. At the end of Stage 1, participants who demonstrate adherence $\leq$95% will undergo a second randomization to either stay in their original group or receive the stepped up intervention. The primary outcome is electronically-monitored adherence. Secondary outcomes include seizure severity/frequency, quality of life and healthcare utilization. These data will then be examined, analyzed, and used to evaluate study aims including efficacy, effectiveness, and predictors of treatment responsiveness.

## 2. PURPOSE OF STUDY

The purpose of this study is to evaluate the efficacy of a mHealth adherence intervention in caregivers of children with newly diagnosed epilepsy, to compare the effectiveness of three different intervention strategies, and to identify predictors of treatment responsiveness.

Specifically, our aims are as follows:

Aim 1: Examine the efficacy of the mHealth adherence intervention in caregivers of children (ages 2-12) with newly diagnosed epilepsy (< 2 years) on electronically monitored adherence.

Aim 2: To compare the effectiveness of the three intervention strategies on adherence, seizure severity/frequency, quality of life, and healthcare utilization at 1-, 6-, and 12-months post-intervention.

Aim 3: To identify individual and family characteristics that predict responsiveness to the three intervention strategies and to derive an optimal, adaptive intervention strategy for tailoring selection of initial and subsequent intervention in the case of nonresponse based on individual characteristics.

## 3. BACKGROUND

**Children with epilepsy represent a high-risk and underserved population.** Epilepsy is a common chronic neurological condition that affects 1%[2] of the US population and disproportionately affects children[3] (750,000 youth).[4,5] Epilepsy is characterized by recurrent unprovoked seizures. Children with epilepsy are 3-6 times more likely to have neurodevelopmental (e.g., autism) disorders,[6] and/or psychological (e.g., depression) comorbidities than the general population and children with non-neurological conditions.[7-10] Children with epilepsy are at 4-fold increased risk[11] for premature death, with higher risk linked to comorbidities.[11-14] Further, 54-59% of youth with epilepsy live in poverty (i.e., household income < $36,000),[15-17] 53% have public insurance,[16] 32% live in rural locations,[17] and 64% of caregivers have low health literacy.[15] Unfortunately, federal programs/agencies have historically allocated considerably less funding to epilepsy than far less prevalent conditions.[18]

**Despite the heavy burden of epilepsy[4], children with epilepsy are an underserved and vulnerable population with many unmet medical and behavioral health needs.**[18,34-39] Only 30% of children with epilepsy receive psychosocial/behavioral health care including adherence interventions, likely due to barriers inherent in the delivery or context of the intervention itself.[34,35] Furthermore, ~60% of children with newly diagnosed epilepsy and their caregivers demonstrate non-adherence,[40] a significant risk factor for poor health outcomes. In particular, children with lower socioeconomic,[40] African American race status,[41] and lower parental health literacy[15] are at increased risk for antiepileptic drug (AED) non-adherence. This may be due to greater concerns about the AEDs, including whether they are more harmful than beneficial.[42] Similarly, lower socioeconomic status, African American race, and rural residency are associated with increased risk of early death,[11,17] likely due to lack of resources and access to comprehensive multidisciplinary epilepsy care.[38,43] Overall, these findings highlight that children with epilepsy are an underserved population, with some subgroups exhibiting multiple risk-factors and vulnerabilities contributing to non-adherence.

**Consequences of non-adherence are significant.** Non-adherence makes seizure control more difficult,[44,45] leading to increased healthcare utilization,[46,47] unnecessary AED changes,[48] and even death.[13] Children who demonstrate AED non-adherence in the first six months of treatment are >3 times more likely to have seizures 4-years post-diagnosis compared to children with near-perfect adherence.[45] Our research also demonstrates that both biology and adherence play critical roles in health outcomes and that variable non-adherence appears to increase the likelihood of having seizures.[44] Non-adherence has also been shown to impact patient-reported outcomes (e.g., quality of life).[49] Despite the known impact of non-adherence on health and patient-reported outcomes for children with epilepsy, few adherence interventions have been developed.

**Adherence interventions are critically necessary, need to target caregivers, and must be individualized.** A 2017 Cochrane review indicated a lack of well-designed randomized controlled clinical trials (RCT) to improve adherence in epilepsy, especially in young children.[50]

Based on this Cochrane review, we are the only researchers to develop and pilot test interventions for young children with epilepsy and their caregivers. In our first pilot study, families receiving an education and problem-solving intervention had a 32% adherence improvement from baseline to post-intervention.[51] In the second pilot study, statistically significant differences between treatment versus controls were noted following the second problem-solving session.[52] Both interventions focused on education and problem-solving and demonstrated excellent preliminary efficacy and feasibility/acceptability among families. The problem-solving approach targeted family-specific adherence barriers, which varied by family, suggesting the need for individualized treatment. Furthermore, improvement in adherence varied based on the number and types of barriers endorsed. For example, some families who endorsed forgetting chose text reminders and had significantly improved adherence while others required further problem-solving around more difficult barriers, such as behavior problems. This highlights the need for both tailored and stepped up care to match the family's specific barriers and needs. Further, scheduling face-to-face sessions was challenging; thus, a model utilizing mHealth could improve dissemination of adherence interventions. The proposed intervention will translate the education and problem-solving content from our pilot studies to mHealth modules for families. Notably, these modules will be provided in a stepped up care approach, such that non-responders will receive more time and resource-intensive problem-solving sessions followed by therapist-guided telehealth sessions to address family-identified adherence barriers.

**Targets for adherence intervention.** Previously identified targets for adherence intervention in young children with epilepsy and their caregivers include epilepsy knowledge, adherence barriers (e.g., forgetting to take AEDs), problem-solving, communication, and effective self-management skills.[52-54] These studies highlight that we have identified optimal targets (mechanisms of action) for the proposed intervention.

**Knowledge:** Caregivers of children with epilepsy reported lacking information about their child's epilepsy.[55] Only 29% of caregivers of children with epilepsy knew the name or dose of their child's AED,[56] and some did not believe that AEDs were beneficial.[57-59] Increasing adult knowledge of epilepsy and the perceived benefits of AEDs may be associated with adherence gains.[60-63] However, knowledge is necessary but not sufficient to improve and sustain treatment adherence.[64-66] Teaching children and families the skills to apply this knowledge (e.g., how to implement an AED titration schedule, when to take AEDs) is critical to improve adherence and will be provided to both control and treatment groups in the current proposal.

**Forgetting:** Forgetting is a major adherence barrier across many pediatric and adult chronic conditions.[42,59] mHealth solutions may address this barrier because 92% of adults have cell phones (67% are smartphones), with 97% using text messaging and 89% using it for the internet.[67] Individuals with lower income or of minority status increasingly depend on smartphones for internet access.[67] As such, the number of mHealth tools focused on improving adherence via automated digital reminders have increased, with 160 commercial adherence tools currently available.[68] These reminder systems have high feasibility, satisfaction, cultural acceptability, ease of use, and are low-cost. A recent meta-analysis of text-messaging interventions to improve adherence revealed significant benefits in 18 of 29 studies; however, only three of the 18 studies were pediatric and none were in epilepsy.[69] Another review of electronic medication packaging and digital reminders found variable improvements in adherence, but studies lacked scientific rigor (e.g., small sample, non-randomization) and were primarily adult-focused.[70] Notably, both reviews concluded that long-term rigorous RCTs, with objective adherence measures, are still needed to determine the efficacy of mHealth adherence interventions, especially in pediatrics. Further, a 2017 review of all mHealth pediatric interventions found that caregiver involvement was a significant positive moderator of treatment effects, suggesting the need to focus on caregivers of children with chronic diseases.[71]

**Individualized Adherence Feedback:** These meta analyses also found that the best performing interventions tailored content to the specific needs of an individual,[69] indicating that

individualized adherence feedback is critical to the success of this type of intervention. For example, an HIV adherence intervention study that provided electronically-monitored adherence feedback to non-adherent patients (< 95%) found a 10% improvement (i.e., 86.8% to 96.5%) in the treatment group versus 1% improvement (83.8% to 84.5%) in the control group.[72] Interventions using individualized feedback in pediatric asthma have also resulted in short-term adherence improvements.[73,74] Several adult studies have demonstrated significant improvements in adherence relative to control conditions with the provision of individualized adherence feedback,[75] suggesting this is a beneficial method to improve adherence in caregivers of children with epilepsy.

**Problem-solving:** Beyond forgetting, caregivers of children with epilepsy identify general barriers, including competing extracurricular activities, difficulty swallowing pills, and poor family communication, as well as epilepsy-specific barriers such as AED side effects and the stigma associated with having epilepsy and taking AEDs.[59] Tailored problem-solving around these more complex adherence barriers can be provided to children with epilepsy and their caregivers who most need it. For example, if caregivers report oppositional behaviors as a primary barrier, problem-solving would focus on identifying solutions, such as giving rewards for taking AEDs, to reduce oppositional behaviors. Our intervention studies demonstrate that face-to-face problem-solving is efficacious in improving adherence but does not reach many families with children with epilepsy. Thus, one goal of this proposal is to translate problem-solving content into a mHealth module with therapist-guided telehealth sessions. These problem-solving sessions require trained professionals; thus, this component is reserved for participants who are non-responsive to the initial, less time-intensive and costly adherence intervention dose (e.g., automated digital reminders, individualized adherence feedback) and need stepped-up, tailored care. Because clinician time is not required for the initial intervention, our intervention has considerable potential for sustainability and broad dissemination for epilepsy and other chronic conditions.

**Overall Impact.** If successful, the results of this study would have a large impact on pediatric epilepsy and other chronic pediatric conditions, with the potential to change clinical practice for treating non-adherence. The provision of mHealth adherence interventions will have greater reach, especially to those at highest risk within pediatric epilepsy, reducing common barriers to behavioral health care. The study design will allow us to identify patients who are most likely to respond to interventions and step up care with more time- and resource-intensive interventions (i.e., therapist-guided telehealth sessions), when necessary. In the future, front-line health care providers, including nurses and social workers, could provide these therapist-assisted telehealth sessions. A tailored intervention that uses minimal resources will also maximize cost-savings. If efficacious, mHealth adherence interventions could be presented proactively to caregivers at diagnosis to promote high adherence behaviors initially, resulting in substantial cost-savings and prevention of poor health outcomes.

Our group conducted the first aims of this grant, in which we conducted focus groups and usability testing across the four sites to develop the Education microlearning sessions, Problem-solving module, and individualized adherence feedback reports with input from caregivers of young children with epilepsy. Their input provide significant feedback related to the design and infrastructure of the intervention, which directly informs this SMART trial.

## 4. STUDY DESIGN

We are conducting a sequential, multiple assignment, randomized clinical trial with caregivers of youth with epilepsy (n=600) in order to evaluate the efficacy and effectiveness of a mobile health adherence intervention to improve adherence to antiepileptic medications in children with newly diagnosed epilepsy. For the purposes of this protocol, CCHMC will serve as the Primary Site. The term “Collaborating Site” refers to external children’s hospital sites working in

collaboration with CCHMC on the study, including Medical University of South Carolina, Nationwide Children's Hospital, and Children's Hospital of Orange County.

## 5. DURATION

The anticipated duration of the study is approximately 5 years. The duration for participants is variable depending on their level of adherence during the baseline period and their enrollment date as the follow-up period was shortened twice to continue enrollment and allow participants to complete the study by the end of the grant period.

- For enrolled participants who achieve electronically monitored adherence >95% in the baseline period, their study participation will be approximately 2 months, with conclusion at the end of the baseline period.
- For participants with adherence ≤ 95% in the baseline period, their participation will be:
  - 20 months (2 months baseline, 5 months of active intervention, and 13 months of follow-up) if they enrolled before 12/9/2022.
  - 14 Months (2 months baseline, 5 months of active intervention, and 7 months of follow-up) if they enrolled between 12/9/2022 and 3/8/2023.
  - 8 months (2 months baseline, 5 months of active intervention, and 1 month of follow-up) if they enroll after 3/8/2023.

## 6. SELECTION & RECRUITMENT OF PARTICIPANTS

### *Study Participants*

Study participants will include up to 600 caregivers of youth with epilepsy between 2-12 years old at CCHMC and collaborating sites. Caregivers will be recruited during routine medical appointments with neurology or epilepsy-related hospital visits and will meet the following inclusion/exclusion criteria:

**Inclusion criteria**

- Child age 2-12 years old
- Diagnosis of epilepsy within the last 2 years
- On ≤2 antiepileptic drugs (AEDs)
- Ability to read and speak English

**Exclusion criteria**

- Diagnosis of non-epilepsy medical disorders requiring daily medications (Asthma, allergies, ADHD, and daily vitamins are okay)
- Diagnosis of severe behavioral disruption, developmental delays (global), and Autism Spectrum Disorder (DSM 5 Level 2 or 3 severity) based on medical chart review and/or parent report. "Severe" is defined as children who:
  1) have an IQ < 70 if documented
  2) are nonverbal
  3) have impaired thinking
  4) have aggressive behaviors
  5) have "global developmental delay"
  6) use a school aide (i.e. someone providing 1:1 help in the classroom)

### *Recruitment Procedures*

Potential participants meeting eligibility criteria will be identified by a trained research coordinator in collaboration with the epilepsy team. If potential participants are eligible, a trained research coordinator will approach families during their medical clinic visit. A thorough overview of the study will be provided, including study procedures, benefits, and risks. *Research coordinators will verify all inclusion/exclusion criteria as noted above.* A study figure will also be given to families to understand the design and timeline of the trial (See Appendix A). All questions will be addressed and informed consent/assent will be obtained (see Section 7).

Following informed consent from the caregiver/legal guardian and child assent (11 years and older), electronic pillbox and pill bottles will be provided, and baseline questionnaires will be completed via REDCap. The recruitment script can be found in Appendix B and other recruitment materials can also be found in the appendices, including flyers, study magnets (Appendix C). Recruitment materials will be used in various places to help recruit participants (e.g. flyers posted on hospital specific social media sites, distributed in clinic, etc.). Notably, this trial is focused on serving at least 30% of those that are underrepresented. Underrepresentation is defined as minority race/ethnicity, public/no insurance status, and living in a region that is rural or medically underserved based on HRSA maps. We will track the number of participants that meet these criteria throughout the trial to ensure at least 30% of our participants are underrepresented. The medical chart review will provide data on this status.

## 7. PROCESS OF OBTAINING CONSENT

As noted above, once participants are identified as study eligible, they will be approached during their epilepsy clinic visit and provided a description of the study (e.g., study procedures, benefits, risks) by a trained research coordinator included on the approved IRB protocol. After addressing all questions from potential participants, informed consent/assent will be obtained by trained research staff. Consent forms will be signed electronically using REDCap, a secure web- based interface supported by the CCHMC Division of Biomedical Informatics in compliance with HIPAA designed to protect PHI in the electronic transfer and storage of the consent form.
Should technical issues arise with the REDCap interface, hard copies of consent forms may also be used. For all consent visits, all pertinent aspects of consent will be covered including study purpose, risks/benefits, confidentiality, and right to withdraw. Patients will be informed that their care at CCHMC or other collaborating study sites will not be affected by whether they choose to participate in the study.

If the caregiver agrees to participate and is signing an electronic consent form via REDCap, they will have an opportunity to check a box stating that they agree to provide their consent. There will also be fields for their typed name, date, and electronic signature to document the informed consent process. Once the electronic form has been submitted, caregivers will receive a copy of the electronically signed and dated consent form via email.

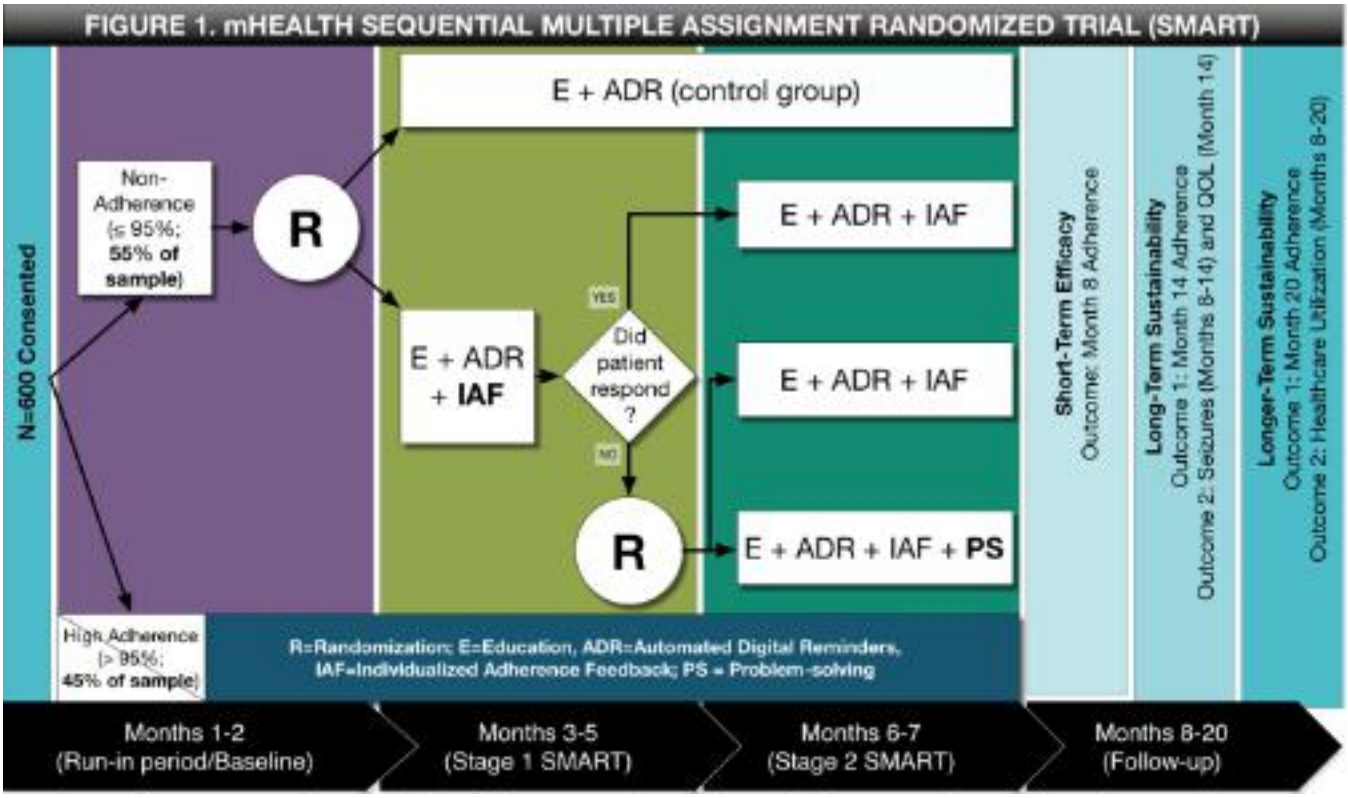
Participants recruited in-person will complete the informed consent document in-person. For participants who decide to participate after the clinic visit, we will use telephonic electronic consent. Specifically, a member of the study team will provide a link to access the consent form in REDCap via email or text message. A hard copy of the consent form may also be mailed if necessary. During the consent/assent phone call, research staff will ensure all questions are answered. In compliance with CCHMC SOP Number 41-1.6, study staff will sign and date accordingly on the signature page of each form corresponding to the date the forms were received, not necessarily reviewed with the family. The method used to obtain participant consent will also be written on the Informed Consent Process Note.

## 8. STUDY PROCEDURES

This is a longitudinal study of caregivers of children with epilepsy that will employ SMART methodology to test the efficacy and effectiveness of a mHealth adherence intervention. Potential participants will be identified by the study coordinator in collaboration with the epilepsy team at each site as noted above. After caregivers provide informed consent (see Section 7), baseline questionnaires will be completed via REDCap, including a demographics form and study measure questionnaires (see Measures section below). All measures will be hosted on REDCap, a secure web-based interface. The PI and her team have fully tested REDCap questionnaires and will test prior to study implementation across all sites to ensure functionality. A medical chart review will also be conducted to gather information about seizures, medications,

seizure etiology, comorbidities, and time since diagnosis. It is notable that the participant must provide an email address for the online questionnaires. If they do not have one, we will help them create one or we will text the link to their cellular phones, if needed.

The eACT SMART design is illustrated in Figure 1 below. All participant families will complete a 2-month baseline period during which they will use electronic adherence monitoring (i.e., pillbox or pill bottle) to measures adherence. Participants who demonstrate adherence $\leq$ 95% will move on to Stage 1 SMART for randomization. In SMART Stage 1 (3-months), caregivers will be randomized to control group (mHealth education microlearning sessions and module and automated digital reminders) or treatment (control condition plus individualized adherence feedback reports)




- **Education microlearning sessions:** The 4-5 education microlearning sessions will take approximately 5-10 minutes to complete on any mobile device, tablet or computer. All caregivers will be provided with a link to the portal with their log-in information following the baseline period to obtain access to the microlearning sessions. These sessions have information regarding the diagnosis of epilepsy, treatment, rationale for adherence, and other epilepsy facts that caregivers have found beneficial.

- **Automated Digital Reminders** – Each adherence electronic monitor has the capability to provide automated digital reminders. As a part of the intervention, all caregivers randomized to intervention will have to option of selecting the type of automated digital reminders that they receive, which could include text messages and/or device sounds/lights. These will be turned on immediately following the baseline period based on the participant's preferences.

- **Individualized Adherence Feedback Reports** - Individualized adherence feedback will be received by families once a week where they will be provided with information about

adherence levels over the previous 7 days based on their electronic adherence monitors. All individualized adherence feedback reports will be received on Monday. A separate portal has been developed by Bioinformatics at CCHMC to create the adherence feedback reports. Data from the SimpleMed pillbox via open API and AdhereTech via excel spreadsheets are merged to provide a calendar plot with the participant's adherence data from the past week. The participant will receive a push notification to view their adherence from the past week. The portal with this information will use the same log-in information as the education and problem-solving sessions. It is notable that the participant must provide a cell phone number for the push notifications.

At the beginning of SMART Stage 2 (2-months), caregivers randomized to the treatment group who demonstrate continued non-adherence (≤95%; non-response) by the end of Stage 1 will undergo a second randomization to either 1) continued individualized adherence feedback or 2) individualized adherence feedback augmented with a mHealth problem-solving module and two therapist-guided sessions using Zoom for healthcare. The mHealth problem-solving module incorporates a video and reviews skills of problem-solving for caregivers of young children with epilepsy and takes approximately 10 minutes to view from any mobile device, tablet or computer. The same log-in information for the education microlearning sessions will be used to access the problem solving modules. Following completion of the problem-solving module, a therapist will contact the family to review and apply the problem-solving skills. Two sessions will occur one month apart via teleconferencing (i.e., Zoom for Healthcare-Appendix D), which is a HIPAA-compliant teleconferencing site.

After completion of Stage 2, automated digital reminders will be turned off and adherence feedback reports will cease to be provided. Additional questionnaires will be completed via REDCap at Post-Treatment (1-Month Follow-Up in Month 8), Follow-Up 1 (6 months post-treatment in Month 14)*, and Follow-Up 2 (12 months post-treatment in Month 20)**.

***Data collection procedures and measures:*** Participants will complete a demographic questionnaire that provides general information about the child's age, caregiver work history, family composition, socio-economic status, family history of seizures, history of seizures (e.g., type, who witness, when they occurred), and comorbid illnesses (e.g., learning disorders). In addition, caregivers will complete the questionnaires detailed in the table below.

| **Construct Measured** | **Respondent** | **Stages and Time points** | | | |
|---|---|---|---|---|---|
| | **C=Caregiver; M=Medical Chart Review D=Doctor/Clinician** | *Baseline* | *Post (1 month post-treatment)* | *Follow-Up 1 (6 months post-treatment) ** | *Follow-Up 2 (12 months post-treatment) *** |
| ORDER OF MEASURES (As applicable) | | | | | |
| Background Form (Demographic) | C | X | | | |
| Pediatric Epilepsy Medication Self-Management Questionnaire (PEMSQ)<br>• PEMSQ: Self-reported Adherence | C | X | X | X | X |
| Behavior Assessment System for Children-3 Parent-Rating Scales | C | X | X | X | X |
| Short Test of Functional Health Literacy in Adults | C | X | X | X | X |
| Pediatric Quality of Life in Epilepsy Module | C | X | X | X | X |
| Brief Symptom Inventory-18 (BSI-18) | C | X | X | X | X |
| Epilepsy Knowledge Questionnaire-Adapted (EKQ) | C | X | X | X | X |

| | | | | | |
|---|---|---|---|---|---|
| Social Problem-Solving Inventory-Revised Short (SPSI-Revised Short) | C | X | X | X | X |
| Pediatric Epilepsy Side Effects Questionnaire (PESQ) | C | X | X | X | X |
| Seizure Severity Scale Adapted for Children (SSSC) | C | X | X | X | X |
| Family Assessment Device (FAD) | C | X | X | X | X |
| Global Assessment of the Severity Scale of Epilepsy in Children (GASE) | D | X | X | X | X |
| Healthcare utilization | C | X | X | X | X |
| Medical Chart Review | M | X | X | X | X |
| Feasibility/Acceptability Questionnaire (FAQ) | C | | X | | |
| Impact of COVID-19 on Pediatric Epilepsy Management (ICPEM) | C | X | X | X | X |

*Follow-Up 1 Questionnaires will only be completed by participants enrolled before 3/8/2023
**Follow-Up 2 Questionnaires will only be completed by participants enrolled before 12/9/2022

An additional questionnaire related to the child's seizure severity (one item) will be obtained from the child's epilepsy provider. A medical chart review will also be conducted to describe key patient medical characteristics (e.g., epilepsy type and treatment, seizure frequency, quality of life, side effects, hospitalizations, emergency room visits, and telephone contacts to clinic staff between routine clinic visits). Chart reviews will cover the entire study period. *Due to the unexpected COVID-19 pandemic, we are also including a newly-developed measure, the Impact of COVID-19 on Pediatric Epilepsy Management (ICPEM) to understand how COVID-19 is impacting our research participants and the outcomes of our study*.

Raw adherence data will be obtained from the SimpleMed pillbox and AdhereTech bottles and will be used as the primary outcome variable. Data from these devices is obtained real-time via blue-tooth and 4G technology and thus will require no additional burden for participants. They will simply put their anti-seizure medicine in the electronic monitor (those who already use bottles will be given an AdhereTech bottle and those who use pillboxes will be given SimpleMed pillboxes).

To increase retention, we will be sending thank you letters, birthday cards and holiday cards (See Appendix E). We will also be providing all participants with a study folder with materials that may be helpful during the study, such as an introductory letter, study timeline, information about their electronic monitor, and our contact information (See Appendix F).

***8.1 Sample Size Considerations and Power Analysis:*** Power analysis was conducted based on SMART Stage 1, assuming ~180 participants randomized to treatment and ~90 to control group. Effect sizes for education-focused adherence interventions with reminders in other chronic conditions relative to controls (e.g., treatment as usual, pre-post) range from 0.08-0.20,[72,170] while those with adherence feedback range from 0.78-1.03.[80,171] Power for the primary analysis (Aim 1 below) will be 80% to detect a small-to-moderate standardized effect size (Cohen's d=0.36) and 97% to detect a moderate standardized effect size (Cohen's d=0.50). These detectable effect sizes reflect clinically meaningful changes in adherence. Power analyses require known and unknown assumptions, such as the anticipated response rate to Education + Automated Digital Reminders + Individualized Adherence Feedback at the end of Stage 1. Effect sizes for our face-to-face problem-solving adherence intervention, which incorporates IAF relative to treatment as usual, ranged from 0.95 (1$^{st}$ problem-solving session) to 1.59 (2$^{nd}$ problem-solving session).[15] Assuming a 50% response rate to SMART Stage 1 treatment and a Bonferroni multiplicity adjustment, the proposed sample size provides 80% power with alpha at 0.05 to detect a standardized effect size of d=0.69 between any pair of embedded strategies (SMART Stage 2).

***8.2. Data Analysis:*** All data analysis and management will also occur at North Carolina State University (NC State), which is the primary data analysis site. The Division of Behavioral Medicine and Clinical Psychology at CCHMC has developed a Divisional Data Core (DDC) in cooperation with the divisions of Biostatistics and Epidemiology and Bioinformatics to share the de-identified data with NC State. The CCHMC DDC will provide quality reports to audit the data routinely, provide data for safety monitoring committee reports for the biostatisticians at NC State, and cleaning of the data.

**Aim 1: Examine the efficacy of the mHealth adherence intervention in caregivers of children (ages 2-12) with newly diagnosed epilepsy (< 2 years) on electronically monitored adherence.** Electronically-monitored adherence, measured on a scale of 0-100%, will be calculated for the final 30 days of Stage 1 SMART. The primary outcome is percent change in adherence from baseline, calculated using the baseline and final 30-day adherence. The primary hypothesis is that participants initially randomized to treatment (E+ADR+IAF) will exhibit significantly greater improvements in adherence compared to those randomized to control (E+ADR) from baseline to end of Stage 1 (i.e., last 30 days). A two-sided, two-sample t- test with unequal sample sizes will be used for the primary analysis. *Exploratory Analyses:* Daily electronically-monitored adherence will be available on each participant throughout the SMART. To gain insight into the possible differences in the evolution of adherence following introduction of each intervention strategy, we will use functional data analysis methods[172] to evaluate and contrast patterns of longitudinal adherence. Functional principal components will be used to estimate a small set of representative adherence patterns associated with each treatment; these patterns will improve understanding of patient trajectories and inform future interventions (e.g., identifying when ADR might be most effective).

**Aim 2: To compare the effectiveness of the three intervention strategies on adherence, seizure severity/frequency, quality of life, and healthcare utilization at 1-, 6-, and 12-months post-intervention.** We will carry out secondary analyses to compare the three intervention strategies embedded in the SMART: #1 E+ADR (control), continuing regardless of response at three months; #2 E+ADR+IAF (treatment), continuing regardless of response; and #3 E+ADR+IAF+Problem-solving if not responsive. Strategies #1 and #2 are non-adaptive intervention strategies in that treatment is not modified in accordance with response status (or any other participant characteristics); #3 is an adaptive intervention strategy in that treatment is augmented by problem-solving only among non-responders. The pairwise comparison of the non-adaptive strategy #1 to the adaptive strategy #3 represents comparison of the least resource-intensive, least burdensome strategy to the most resource-intensive, most burdensome strategy. Note that the actual experience of a participant may be consistent with more than one embedded strategy; in particular, a participant who receives E+ADR+IAF initially, responds, and continues to receive E+ADR+IAF is consistent with having followed either strategy #2 or #3. Thus, such a participant's data contribute to assessment of improvement in adherence for both of these strategies. Comparison of strategies #1, #2, and #3 requires the use of specialized methods[133] that account for the fact that actual experiences of participants may be consistent with more than one strategy. We will conduct pairwise comparisons of the three embedded strategies on the basis of adherence, seizure severity/frequency, quality of life, and healthcare utilization at 1-, 6-, and 12-months post-intervention. Appropriate methods will be used based on the type of outcome measure: binary, count, and continuous variables.

**Aim 3: To identify individual and family characteristics that predict responsiveness to the three intervention strategies and to derive an optimal, adaptive intervention strategy for tailoring selection of initial and subsequent intervention in the case of nonresponse based on individual characteristics.** The data collected in the SMART will provide a rich resource for investigating participant baseline characteristics and post-randomization characteristics ascertained prior to response status that can inform tailored selection of initial (E+ADR+IAF or control) and subsequent adherence strategies (continue E+ADR+IAF or augment with problem-solving) for children who do not initially respond to E+ADR+IAF. We will

carry out several exploratory, hypothesis-generating analyses. We will use standard methods based on linear models for percent improvement in adherence to evaluate baseline characteristics that are moderators of participants' adherence status following initial intervention. We will also use standard tests for qualitative interactions[173] and more recent variable selection methods for qualitative interactions that adjust for multiplicity.[174,175] Evaluation of moderators of outcomes at 1-, 6-, and 12-months post-intervention is complicated by the sequential nature of the interventions, requiring the use of specialized statistical methods. We will use Q-learning[176] and value-search estimation[129,130] to test for moderators of the initial and stepped up interventions. We will first conduct an overall test of the null hypothesis that there are no moderators at either stage. If the test rejects this null hypothesis, we will conduct appropriate multiplicity-adjusted statistical tests to identify specific baseline and intermediate moderators of outcomes at 1-, 6-, and 12-month follow-ups. Because of the sequential nature of the interventions, standard statistical tests are invalid without appropriate modification.[132,177] We will use suitable bootstrap methods to ensure that the tests are valid (i.e., have correct control for Type 1 error). We will also use Q-learning and value-search estimation[111,112] to estimate an optimal adaptive intervention strategy for personalizing selection of initial intervention and the need for stepped up care following E+ADR+IAF based on child/caregiver characteristics. We will evaluate the potential improvement in adherence that could have been realized for each participant in the SMART if s/he had received initial and secondary interventions via the optimal adaptive intervention strategy. We will also carry out Monte Carlo simulations to compare the average percent improvement in adherence achievable using the optimal adaptive intervention strategy to those achievable using the simpler embedded strategies #1- #3. This analysis will provide valuable insight on key characteristics implicated in heterogeneous intervention effects and subgroups and form the basis for formulation of personalized intervention strategies for subsequent study.

## 9. POTENTIAL BENEFITS

No immediate or direct benefits to patients participating in this study are expected. However, it is possible that participants will learn more information about epilepsy and have improved adherence. The information obtained from this study can ultimately be used to increase knowledge in the scientific community about how to improve adherence in diverse youth with epilepsy.

## 10. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES, & PRECAUTIONS

There are minimal potential risks/discomforts/inconveniences to participants in this study, no greater than those encountered in routine behavioral assessment and clinical care. There are no medical risks. All the questionnaires have been used in research, including our own, without any reported negative effects; however, it is possible that a small group may feel uncomfortable responding to questions. Participants may decline answering questions that cause them to feel uncomfortable and will be reminded of this prior to each study visit. Participants may also withdraw from the study at any time and will be informed of this right during the consent process.

If a participant is distressed by any study procedures, the site PI or designee (CCHMC- Avani C. Modi, PhD or Shanna Guilfoyle, Ph.D., licensed clinical psychologists) at CCHMC will be contacted immediately to assess the situation. The study PI or their designee will provide appropriate referrals and/or intervention. In addition, questions on the questionnaires inquire about suicidal ideation by the caregiver, as well as the caregiver's perception of suicidal ideation for their child. These critical items are automatically flagged by the REDCap system, which will alert the clinical research coordinator at each site when a participant completes the questionnaire and endorses critical risk items. Safety procedures for suicidal ideation and reports of abuse/neglect are delineated in our safety monitoring committee plan (See Appendix G). In both cases and similar to above, the study PI or their designee at each site will be contacted immediately and he/she will assess the risk profile of the caregiver and/or child participant with subsequent recommendations based on the level of risk.

There is also the risk of possible loss of privacy of data or loss of confidentiality. These risks are inherent in all research studies, and a statement to this effect will be included in the informed consent. Every effort will be made to ensure that all participant information will be kept confidential. A majority of this study is going to be conducted via mHealth. Participants will be accessing or receiving information from several different sources, including REDCap, education/problem solving modules Wordpress site, Zoom for healthcare for Problem-solving with a therapist, a portal created by CCHMC to receive push notifications related to their adherence feedback reports, and the adherence monitoring portals for AdhereTech and SimpleMed. For each of these sites, we will use the participant's ID number and not their name. For example, enrolled participants will be assigned a secure login ID and password by the study staff to access measures via REDCap. Each site will only be able to see their own site's participants in REDCap, with the exception of the lead site (CCHMC). Participants will be asked not to share their ID or password with anyone else. Use of Protected Health Information (PHI) on online measures will be minimized and participants will not be asked to enter their last name, date of birth, or medical record number on the online measures. When the study is complete, the content of the site will be taken down. Setup is consistent with HIPAA guidelines and was designed to support projects that contain PHI and are subsequently subject to compliance with federal and state regulations regarding data of this type. Similarly, the Wordpress site for the modules will be linked to their study ID and there will be no identifying information listed in this site. However, for the individual adherence feedback reports, participants will be asked to provide a cell phone number to receive push notifications. Similarly, although Zoom-healthcare is HIPAA compliant, participants will be required to log-in to the secured Zoom server for Problem-solving sessions. This information and protection of the participant's identify will be clarified in the informed consent and assent forms.

Additionally, we will be geocoding their home address to quantify if the patients live in rural or medically underserved areas using a combination of HRSA maps and an app created by CCHMC. We will obtain parental permission to use the patient's address for this purpose.

Finally, to communicate study related information across sites, our team will be using trello, a task management system that is frequently used by research teams. No identifying information will be entered into the trello system; however, we will be tracking participants through the study procedures using their study ID.

Notably, the only place the study ID will be linked to the name and demographics is the participant database, which is password protected, individually, at each site by the research team. No other individuals outside of the IRB-approved research team will have access to this participant database and these databases will NOT be shared across study sites.

## 11. RISK/BENEFIT ANALYSIS

There is minimal risk associated with study participation. If participants feel distressed as a result of their participation, they will be encouraged to discontinue. The PI (Avani C. Modi, PhD) and site PIs or their designee will be available to participants during study participation to assess for discomfort, safety, and risk, as needed. The minimal risks of this study do not outweigh the potential indirect benefits that may be gained through increasing knowledge about best practices for improving adherence to treatment and quality of life of children with pediatric epilepsy.

## 12. DATA SAFETY AND MONITORING

This is a multisite observational study and is considered minimal risk. A Safety Monitoring Committee (SMC) is in place for this study and will review randomization, safety events, and study progress every 6 months following trial initiation. In addition, each site's research team will monitor for safety and adverse events at each study visit. The SMC plan, which was approved by the National Institutes of Nursing Research, is attached in Appendix G. Dr. Modi (PI) and site PIs, and the members of the Data Safety Monitoring Plan will be responsible for monitoring the

safety of participants and complying with all reporting requirements. Any serious adverse events will be reported immediately to the IRB as required by the hospital's policy, as well as NINR.

## 13. PRIVACY AND CONFIDENTIALITY

All study personnel have been trained in data safety and monitoring, privacy and confidentiality, minimizing risks related to loss of privacy and confidentiality. We will closely monitor performance of our research personnel to ensure the strictest standards. Additional information related to privacy and confidentiality is noted above in section 10.

***13.1 Data De-Identification*:** All data will be de-identified with the use of unique assigned study identifier codes. No other identifying data such as address, phone numbers, social security number, or zip code will be entered on electronic measures. Electronic data files (including downloads of data from REDCap measures) will only identify participants via study identifier codes and will be password protected. Electronic data files will be maintained on CCHMC hard drives.

Because this research study involves payment for participation, we are required by Internal Revenue Service (IRS) rules to collect and use participant's social security number (SSN) or taxpayer identification number (TIN) in order to track the amount of money that we pay them. Unless they have given specific permission for another use of their SSN or TIN related to this research study, we will only use their SSN or TIN to keep track of how much money we pay them and their SSN or TIN will not be used as part of this research study.

***13.2 Data Storage and Management:*** Informed consent documents and all electronically collected data will be maintained in REDcap, a secure web-based platform, and in a password-protected electronic database on CCHMC hard drives. Although CCHMC, as the Primary Site, will be the study management location, no patient information from other sites will be shared other than de-identified IDs. Paper informed consent documents will be maintained in locked storage cabinets, if they are needed, and will be kept separate from participant data.

Deidentified adherence data will be stored on their respective portals (AdhereTech, SimpleMed) and these data will be triangulated with a CCHMC developed portal to provide individualized adherence feedback reports, based on the participant's cell phone number.

Trello (www.trello.com), a web-based project management tool, will be used to coordinate study-related tasks across sites. No identifiable patient information will be saved in this platform. Medical chart data will be collected by trained study staff under the supervision of the PI. These risk protection methods have been effectively used by the PI and her collaborators for numerous studies.

Individual data will not be available to anyone not directly associated with the study. All study personnel have been trained in data safety and monitoring, privacy and confidentiality, minimizing risks related to loss of privacy and confidentiality. We will closely monitor performance of our research personnel to ensure the strictest standards. Study-related information will not be released without written permission of the participant.

## 14. COST OF PARTICIPATION

There are no costs for participation in this research study. Participants will be responsible for the usual costs of medical care.

## 15. PAYMENT FOR PARTICIPATION

Caregivers will be compensated for participation in the study in the form of a reloadable debit card (ClinCard).They will receive a handout that will explain how to use this card. A graduated

incentive schedule will be used:

| Study Task | Compensation |
|---|---|
| Baseline Questionnaires | $20 |
| Post-Intervention Questionnaires | $25 |
| Follow-Up 1 Questionnaires<br>*Only participants enrolled before 3/8/2023 will complete these measures* | $30 |
| Follow-Up 2 Questionnaires<br>*Only participants enrolled before 12/9/2022 will complete these measures* | $35 |
| Use & Return of Electronic Monitoring Device | $40 |
| **TOTAL COMPENSATION** | Up to $150 for participants enrolled before 12/9/2022.<br><br>Up to $115 for participants enrolled between 12/9/2022 and 3/8/2023.<br><br>Up to $85 for participants enrolled after 3/8/2023 |

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