Clinical Trials Title: Behavioral Economics and Adherence in Teens (BEAT!)

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NIH Grant Title: Improving Drug Adherence Using mHealth and Behavioral Economics in Adolescents with Epilepsy (R21NR017633)

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER
STUDY PROTOCOL

Study Title: Beat!: A Clinical Trial

Principal Investigator: Avani C. Modi, Ph.D.

1. ABSTRACT

Non-adherence to antiepileptic drugs (AEDs) is a common problem affecting 58% of youth with epilepsy, with potentially devastating consequences. Adolescents with epilepsy represent a particularly vulnerable group, given their increased independence, decreased parental supervision, higher risk for deficits in organization and memory, busy and changing schedules, low motivation, and increased susceptibility to peer influence. Existing adherence interventions in epilepsy are not designed to meet the unique challenges faced by adolescents, and there are no efficacious interventions for adolescents with epilepsy. Not surprisingly, without efficacious interventions, adherence worsens during adolescence, further increasing the risk of poor health outcomes during this developmental period. Data suggest that automated digital reminders and social norms feedback (i.e., feedback about someone else's behavior related to one's own behavior) could be effective strategies to improve adherence in adolescents with epilepsy. As such, our goal is to test the preliminary efficacy of a mHealth social norms intervention on AED adherence, seizure severity, and health-related quality of life (HRQOL) in adolescents with epilepsy. The first phase of this study (ORBIT Phase 1a-b) is almost complete and includes focus groups, usability testing, and extended formative usage evaluation. Data from these phases guided development of a social norms mHealth adherence intervention, which will be tested in this pilot randomized clinical trial (ORBIT Phase 2). Recruitment for the study will take place at Cincinnati Children's Hospital Medical Center and Nationwide Children's Hospital. Enrolled adolescents and caregivers (n=138) will complete baseline questionnaires and electronically-monitored adherence will be collected during the one month baseline period. Adolescents with epilepsy who demonstrate non-adherence during this baseline (≤95%) will be randomized to either 1) Group 1: control (automated digital reminders and individualized adherence feedback) or 2) Group 2: mHealth social norms (automated digital reminders, individualized adherence feedback, and social norms feedback). Both groups will receive active intervention for five months. Primary (i.e., electronically-monitored adherence) and secondary outcomes (i.e., seizure severity, HRQOL) will be assessed post-treatment and 3 months later, respectively. This project addresses the critical need for evidence-based adherence interventions in a high risk adolescent epilepsy population that have the potential to improve seizure severity and HRQOL. This study lays the foundation for larger clinical trials examining the efficacy of a mHealth social norms adherence intervention to improve adolescent epilepsy outcomes.

2. PURPOSE OF STUDY

The purpose of this study is to evaluate the feasibility, acceptability and preliminary efficacy of a social norms mHealth adherence intervention in adolescents with epilepsy. Specifically, our aims are as follows:

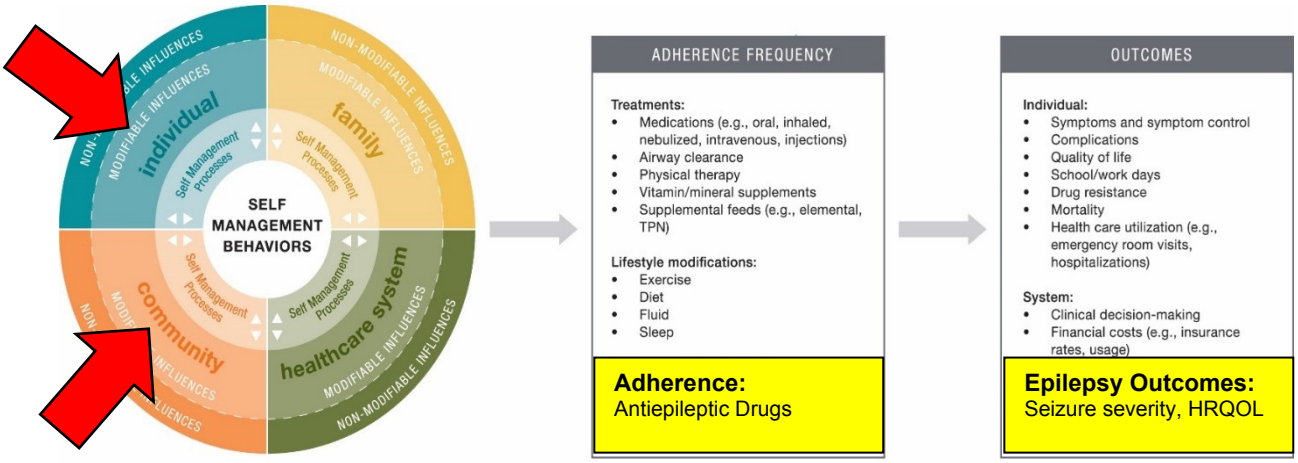
Aim 1: Examine the feasibility, accessibility, acceptability, and responsiveness of a mHealth social norms intervention to improve AED adherence for adolescents with epilepsy. H1: Adolescents with epilepsy will rate the intervention as highly feasible, easy to use, acceptable, and responsive to their needs.

Aim 2: Examine the preliminary efficacy of the mHealth social norms intervention on AED adherence, seizure severity, and HRQOL in adolescents with epilepsy. H2a: Participants in the treatment group will demonstrate statistically significant *improvements* in adherence with corresponding medium/large effect sizes compared to the control group at post-treatment. H2b: Greater improvements in adherence, seizure severity, and HRQOL are expected at 3-month follow-up for the treatment versus control group.

3. BACKGROUND

Adherence is multi-factorial. The Pediatric Self-Management Model (Figure 1) is a comprehensive conceptual model that articulates the individual, family, community, and healthcare system factors that influence self-management behaviors (i.e., the interaction of health behaviors and related processes that patients and families engage in to care for a chronic condition and their subsequent impact on adherence and health outcomes).[25] Adherence behaviors are daily, complex, and multi-factorial. Thus, single component

Figure 1. Pediatric Self-Management Model



interventions are likely to only have minimal effects on adherence,[31, 32] whereas multi-component interventions that influence more than one factor are likely to have greater effects. Our recent review of self-management interventions in pediatric epilepsy, based on this model, concluded that we lack strong evidence for self-management interventions, largely due to small sample size studies or poor design.[16] The focus of this proposal is to address the critical **individual** (i.e., forgetting, motivation, busy schedule) and **community** (i.e., peer influence) factors influencing adherence and self-management in adolescents with epilepsy.

Adolescents with epilepsy represent a high-risk population. Adolescence is often accompanied by susceptibility to peer influence, desire for autonomy, feelings of invincibility, and decreased parental monitoring.[33] Adolescents are motivated by novel experiences and are predisposed to impulsive and risky behaviors due to an immature inhibitory control system.[34] This makes adolescents more likely to engage in behaviors that have immediate rewards, especially in the context of their peers (e.g., skipping taking medication when out with friends), and less likely to be concerned about the negative consequences of their decisions for the future (e.g., having a seizure).[14, 17] Non-adherence to AEDs is a significant problem in adolescence.[35] For adolescents with epilepsy, this is especially difficult due to seizure-related restrictions (e.g., no driving with active seizures) and the need for continued parental supervision to ensure safety (e.g., bathroom door open while bathing[36]), all while self-managing their AED. Seventy percent of adolescents with epilepsy have to be reminded to take their AED; however, they complain that their parents nag them and yet forget to take their AED without

these reminders,[35] suggesting the potential need for more developmentally acceptable alternatives, such as automated digital reminders. While digital reminders are likely beneficial to improve adherence, they are not helpful to adolescents who lack motivation to take their AEDs or abandon use of digital reminders over time (i.e., alarm fatigue[37]). It is well known that adolescence is characterized by strong influences of their peer group, and harnessing these influences may be critical to fostering greater adherence. Thus, additional strategies (e.g., social norms comparisons) that leverage the impact of peer relations may also be necessary to improve and sustain adolescent adherence. Despite the critical need for developmentally appropriate interventions to improve adherence in adolescents with epilepsy,[38] few interventions exist. The limited AED adherence literature[39-43] is characterized by small samples and interventions that are difficult to apply in clinical settings. Further, access to behavioral health providers who can target adherence behavioral change is limited for many adolescents with epilepsy.

Strategies to improve adherence

Social Norms Comparison: A novel approach of applying behavioral economic theories to adherence promotion. Behavioral economics, a scientific field that blends psychology, marketing, and economics to improve individual decision making,[44] is receiving increased attention in healthcare.[45, 46] Behavioral economic theories of decision making posit that social norms comparisons (i.e., feedback about someone else's behavior related to one's own behavior), may increase motivation and thus, be beneficial in improving adherence behaviors in adolescents.[47] Social norms interventions rely upon the large influence of interpersonal factors on human behavior, which is especially salient in adolescence[48]. These interventions involve giving an individual feedback on how he/she performs compared to similar others (community factor of the Pediatric Self-Management Model), which can affect that individual's subsequent behavior. Social norms interventions may exert positive effects through three psychological mechanisms. First, these interventions may provide social proof to the target individual.[7] For example, an adolescent may recognize the importance of taking AEDs consistently when learning that other adolescents have reached this conclusion via the feedback ("You took 10 of 14 doses of your medicine in the past week! However, 4 out of 5 male teens with epilepsy take medication more consistently than you do"). Social norms interventions may also enhance the self-efficacy of the target individual.[8] An adolescent may be convinced that a consistent AED regimen is achievable when learning that other adolescents have already demonstrated high adherence. Finally, social norms interventions may motivate an adolescent to improve his/her standing relative to other adolescents. Many people view themselves as above average in a variety of domains.[9] Therefore, receiving feedback on below average adherence levels may motivate an adolescent to improve the consistency of medication-taking so that these positive self-perceptions can continue to be held. To date, social norms intervention studies have focused on improving clinician performance,[49-51] reducing college students' alcohol consumption,[52] or changing behavior in non-health domains (e.g., energy conservation[53]). Specific to adolescents, social norms interventions are efficacious in decreasing underage drinking,[54, 55] bullying in school,[56] and changing food intake.[57] Recent data focused on health behaviors (e.g., physical activity) in adolescents indicates that social norms interventions have incremental value and improve physical activity above and beyond standard feedback without peer comparisons.[24] Specifically, adolescents who received feedback relative to their peers increased their steps relative to controls who only received feedback on their own behavior and decreased their steps (d=0.41). Further, social norms comparisons yielded significant improvement in academics for adolescents compared to criterion-based feedback (d=0.85).[58] Finally, social norms interventions have been shown to reduce inappropriate antibiotic prescribing,[51, 59] and these effects were maintained even twelve months after primary care clinicians stopped receiving peer comparison reports.[60] Overall, these recent studies

suggest the incremental value of social norms interventions that are clinically meaningful compared to feedback alone, with high potential for long-term benefits.

Because adolescents heavily weigh social pressure, identity, and sense of belonging when making health-related decisions, social norms comparisons may be an ideal method for targeting adherence-related motivation, and as a result, improve adherence among this population.[17, 48, 61] In particular, social norms feedback can provide effective motivation, rarely targeted in adherence interventions,[62] especially for those that perform below average (e.g., poor adherence). Descriptive norms (i.e., obtaining feedback about the average person) can boost performance,[63-65] including adult diabetes adherence behaviors,[66] while injunctive norms (i.e., obtaining feedback regarding the desirability of one's performance) can help to maintain adaptive behaviors[21-23] (e.g., high adherence). Notably, injunctive norms are intended to discourage high adherers from gravitating to the average level of performance.[21, 51] To date, there are no adolescent studies that have applied these principles to improve adherence behaviors. However, as mentioned above, the use of both injunctive and descriptive norms was beneficial in improving adolescent's physical activity (e.g., steps).[24] Our current proposal capitalizes on social norms comparisons to either improve poor adherence or maintain good adherence behaviors in epilepsy, which can then be disseminated to other chronic conditions.

Automated Digital Reminders: In addition to motivation, forgetting is an individual factor of the Pediatric Self-Management model and a primary barrier to adherence across pediatric chronic conditions.[67, 68] While a recent meta-analysis of text-messaging interventions found that 18 of 29 studies significantly improved short-term adherence, only 3 were pediatric focused and none were in epilepsy.[69] Combined with the results of a recent review of digital reminders demonstrating that interventions were promising but lacked scientific rigor,[70] these meta-analyses conclude that long-term rigorous RCTs with objective adherence measures are still needed to determine the efficacy of technology-focused adherence interventions in pediatric epilepsy.

Individualized Adherence Feedback: Given that patients often lack knowledge about their own adherence behaviors and patterns, intervention efficacy may be maximized when feedback is provided and individually-tailored.[69] For example, an HIV adherence intervention study that provided electronically-monitored adherence feedback to non-adherent patients (< 95%) found a 10% improvement (i.e., 87% to 97%) in the treatment group versus 1% improvement (84% to 85%) in the control group.[71] Similar intervention effects have been demonstrated in pediatric asthma[26, 72] and adult heart disease,[73] suggesting this may be a beneficial component for an adherence intervention for adolescents with epilepsy. Our current proposal leverages the benefits of automated digital reminders in improving upon the logistical barrier to forgetting, as well as individualized feedback for improving self-monitoring. However, the inclusion of **social norms comparisons could play a pivotal motivating role to improve adherence behaviors in adolescents with epilepsy.**

mHealth as an optimal vehicle to deliver intervention strategies for adolescents. Mobile Health (mHealth) offers a practical, feasible, culturally and developmentally acceptable, and cost-effective solution for forgetting by enabling the sending and receiving of automated digital reminders (e.g., texts, alerts). Given AED adherence is a daily behavior, mHealth tools also serve as a practical and logistical tool to target motivation by providing adherence feedback, with (treatment group) or without social norms comparisons (control group). A 2013 review identified 160 commercially available adherence tools (i.e., digital reminders and/or medication tracking).[74] mHealth tools are well-matched to the information consumption patterns of adolescents as approximately 90% have cell phones (73% smartphones), 90% of those with cell phones use text messaging,[75] and 91% access the internet on their mobile device (with a notable increase in use for minority youth).[75]

Scientific Premise. Adolescents with epilepsy demonstrate significant AED non-adherence, resulting in poor health outcomes. While adherence strategies exist to improve logistical barriers (e.g., forgetting) for adolescents, no adherence interventions focus on motivation. Use of a mHealth social norms intervention may leverage the important role of peer comparisons to motivate adherence change in adolescents. The proposed approach uses minimal resources (e.g., costs) and has greater reach, especially to adolescents without access to behavioral health care.[76, 77] Because the intervention requires no clinician time and minimal participant burden, our social norms intervention has considerable potential for sustainability and dissemination for multiple pediatric conditions. If successful, study results would have a large impact on pediatric conditions affecting adolescents (e.g., epilepsy), with the potential to change clinical practice for treating non-adherence.

4. STUDY DESIGN

A pilot randomized clinical trial will be conducted in order to evaluate the preliminary efficacy of a mHealth social norms adherence intervention to improve electronically-monitored AED adherence to antiepileptic medications in 138 adolescents with epilepsy. For the purposes of this protocol, CCHMC will serve as the Primary Site. The term "Collaborating Site" refers to the external children's hospital site working in collaboration with CCHMC on the study (Nationwide Children's Hospital).

5. DURATION

Recruitment for the pilot RCT is estimated to take 7 months (approximately 10 patients per month at each site). The duration for participants is variable depending on their level of adherence during the baseline period. For enrolled participants who achieve electronically monitored adherence >95% in the baseline period, their study participation will be approximately 1 month, with conclusion at the end of the baseline period. For participants with adherence ≤95%, their participation will be 9 months (1 month baseline, 5 months of active intervention, and 3 months of follow-up).

6. SELECTION & RECRUITMENT OF PARTICIPANTS

Study Participants

Study participants will include approximately 138 adolescents with epilepsy between 13-17 years old at CCHMC and Nationwide. Adolescents and 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 13-17 years old and their primary caregivers
- On ≤2 antiepileptic drugs (AEDs)
- Ability to read and speak English

Exclusion criteria

- Significant developmental (e.g., autism spectrum disorder, moderate/severe developmental or intellectual disability) or comorbid medical diagnoses (e.g., diabetes)

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. All questions will

be addressed and informed consent/assent will be obtained. Following informed consent from the caregiver/legal guardian and adolescent assent, SimpleMed electronic pillbox (www.vaica.com) and AdhereTech pill bottles (www.adheretech.com) will be provided, and baseline questionnaires will be completed via REDCap or using paper/pencil questionnaires either in person or by mail. Recruitment and retention materials can be found in the appendices, including flyers and study magnets (Appendices A and B and E).

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 collaborating study site will not be affected by whether they choose to participate in the study.

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

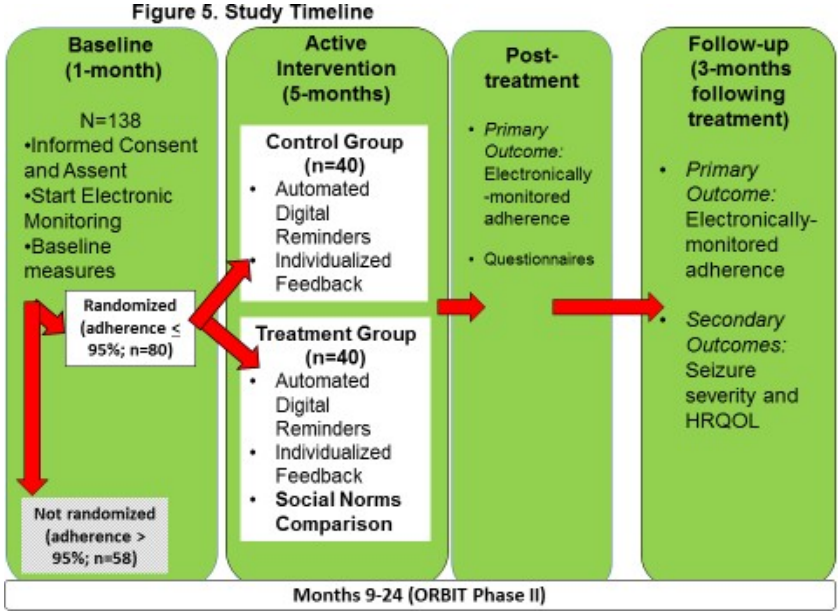
Participants recruited in-person will complete the informed consent document in-person. For participants who decide to participate after the clinic visit, we will use telephonic electronic consent. Specifically, a member of the study team will provide a link to access the consent form in REDCap via email 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 randomized controlled clinical trial to test the efficacy and effectiveness of a social norms 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, baseline questionnaires will be completed via REDCap or using paper/pencil questionnaires (in person or by mail), 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 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 participating caregivers and adolescents must provide an email address for the online or paper/pencil 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 Beat RCT design is illustrated in the Figure below. All participant families will complete a 1-month baseline period during which they will use electronic adherence monitoring (i.e., pillbox or pill bottle) to measures adherence. Participants who demonstrate adherence ≤ 95% will move on to the active intervention for randomization. In the Active Intervention Stage (5-months), adolescents will be randomized to the control group (individualized feedback and automated digital reminders) or the treatment group (control condition plus social norms).

Figure 5. Study Timeline



- **Automated Digital Reminders** – Each adherence electronic monitor has the capability to provide automated digital reminders. As a part of the intervention, all teens randomized to intervention will have to option of selecting the type of automated digital reminders that they receive, which could include text messages (i.e., BEAT Study: This is a reminder for you to take your medicine) and/or device sounds/lights. These will be turned on immediately following the baseline period based on the participant's preferences.

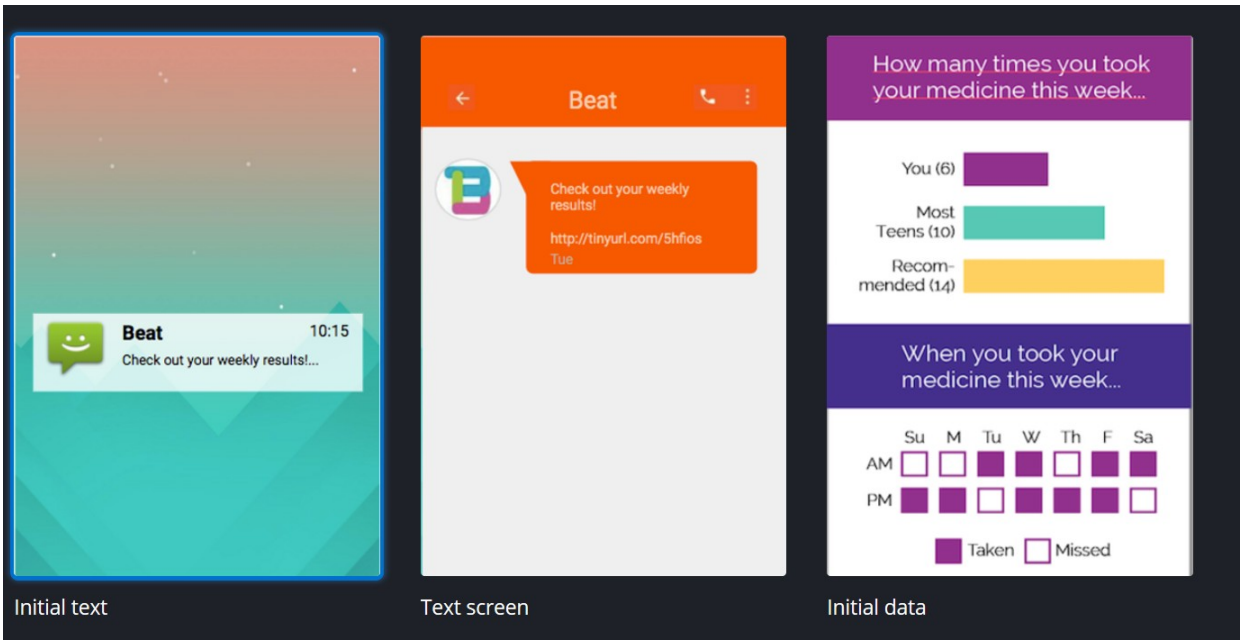
- **Individualized Adherence Feedback Reports** - Individualized adherence feedback will be received by each teen once a week where he/she will be provided with information about his/her adherence levels over the previous 7 days based on his/her electronic adherence monitor. His/her family members and his/her health care providers will NOT receive this individualized adherence feedback from the study team. Outside of study procedures, the adolescent may or may not decide to share this information with those individuals. 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, as well as the social norms feedback reports below. Data from the SimpleMed pillbox via open application programming interface (PI) 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 and these will vary by week (see Table 1). It is notable that the participant must provide a cell phone number for the push notifications.

Alternating Text Messages

1. Check out your weekly results
2. See how you did this week
3. Here are your results for the week
4. Here's your weekly summary
5. Here is how you did last week
6. Please see your weekly results
7. You can find your results for the week here
8. Here are your weekly results
9. Find out how you did for the week
10. Check out your weekly summary
11. Check out your 7-day results
12. See how you do for the last 7 days
13. Here are your results for the last 7 days
14. Here's your 7-day summary
15. Here is how you did for the last 7 days
16. Please see your 7-day results
17. You can find your 7-day results here
18. Here are your 7-day results
19. Find out how you did for the last 7 days
20. Check out your 7-day summary

- **Social Norms Feedback Report** – Individualized social norms feedback will be provided to every teen who is randomized to the treatment group. Specifically, each teen will receive weekly information about how his/her level of adherence over the prior 7 days compares to other teens his/her age based upon previously published research by the PI. Feedback is provided in such a way that the adolescent receiving this feedback will not be able to identify specific individuals comprising the social comparison group. Examples of such feedback include informing the adolescent that "Most other teens with epilepsy …" and "Many other teens with epilepsy." Adolescents will receive this feedback in both written form and visual images. His/her family members and health care providers will NOT receive this social norms feedback from the study team. Outside of study procedures, the adolescent may or may not decide to share this information with those individuals. Data from the SimpleMed pillbox via open API and AdhereTech via excel spreadsheets are merged to provide a graphic representation of how a participant's adherence data from the past week compares to other teens. The participant will receive a push notification to view how their adherence levels compared to other teens. The example below demonstrates how the teen would receive the push notification, which leads to a message in which they need to log-in to a portal with their unique id and password in order to see their adherence feedback (i.e., control group) or social norms adherence feedback report (i.e., treatment group). These images are currently being finalized based on participant feedback from Orbit 1b.

After completion of the active intervention, automated digital reminders will be turned off, adherence feedback reports will cease to be sent, and social norms comparison will no longer be provided. Daily electronic adherence will be monitored until study completion. Additional questionnaires will be completed via REDCap or using paper/pencil questionnaires either in person or by mail at post-treatment (month 7), and 3-month follow- up (month 10).



8.1 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 and adolescents will complete the questionnaires detailed in the table below. 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. See Table 2 for list. 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). As highlighted on their companies' respective websites, the pillbox and bottles feature secure portals for the study team to access adherence data. In addition, the AdhereTech bottles feature a standard child-resistant caps. Instructions for using both devices will be provided to teens (see Appendix D).

Table 2. Questionnaires

	Questionnaire	# of items/Description/Score Used	Reliability/Validity
PRIMARY OUTCOME			
Adherence	SimpleMed+ Pillboxes	Daily objective adherence data; **Score: % Adherence**	N/A
	Self-Report Adherence[91]	1-item adherence item (caregiver and teen); **Score: % Adherence**	MEMS rho=0.46, p<.001
SECONDARY OUTCOMES			
Seizure Severity	Global Assessment of severity of epilepsy (GASE)[106]	1-item clinician report of seizure severity	Clinical vars: (*r*>.30); ROC>.50
	Seizure Severity Scale-Adapted for children[107, 108]	9-item caregiver report of seizure severity (e.g., intrusiveness, frequency, length, disruptiveness). **Score: Total severity**	α = 0.79
Quality of Life	PedsQL Epilepsy Module[93, 109]	29 items representing 5 domains of HRQOL (caregiver and teen); **Scores: Impact, *Cognitive,* Sleep, *Executive Functioning*, and Mood/Behavior scales**	α = 0.75-0.93
COVARIATES			
Side effects	Pediatric Epilepsy Side Effects Questionnaire[110]	19 items assessing typical AED side effects (teen); **Score: Total Side Effect Score**	α = 0.72-0.93
Demographics	Background Form	Child age, sex, and socioeconomic status (caregiver)	N/A
Medical variables	Medical Chart review	Seizure type, etiology, and treatment (e.g., AED)	N/A
COVID-19 Impact	Impact of COVID-19 on Pediatric Epilepsy Management (ICPEM)	*25 item survey regarding personal/familial impact from COVID-19 Pandemic*	*N/A*
MEDIATORS			
Peer Influence[111]	Resistance to Peer Influence Scale	10-item measure with paired statements that best describes situations related to peer influence (teen); **Score: Total Score**	α = 0.74
Adherence Barriers	Pediatric Epilepsy Medication Self-Management Questionnaire[68]	27 items measuring medication self-management (teen and caregiver); **Score: Barriers to Adherence Scale**	α = 0.68-0.85
TREATMENT FEASIBILITY/ACCEPTABILITY/USABILITY			
Usability	*Revised Website/mHealth tool Evaluation Questionnaire (WEQ)[84]*	*8-item open-ended questions regarding the participant's general experience with the mHealth tool, expectations, comfort of use, quality of the tool, connectedness and likes/ dislikes (teen).*	*N/A*
	System Usability Scale[85]	*10-item scale that assessing the usability of an application or mHealth tool (adolescent)*	*N/A*
Feasibility/ Acceptability	*Revised Feasibility and Acceptability Questionnaire[80, 112]*	*37 item survey regarding satisfaction with content, relevance, helpfulness, ease of use, and likeability (teen). Five open ended questions also assess need for modifications and satisfaction.*	*N/A*

8.1 Sample Size Considerations and Power Analysis:

Sufficient Power for RCT: Given timeline and resources proposed for this pilot RCT, we anticipate recruiting N=138 participants. We expect that 58% will have adherence ≤95%, leaving N=80 to be randomized. We conducted a Monte Carlo simulation in Mplus with N = 5000 replications, assuming a total randomized sample of N=80, 25% attrition, proper handling of missing data, standardization of all analysis variables, and that baseline adherence, age, sex, side effects, cognitive/executive functioning, seizure type, and SES (covariates) will explain at least 40% of the post-treatment adherence error variance (based on our pilot data and previous studies[1]) Our analysis indicates that we will have at least 80% power to detect a post-treatment group difference effect size of d > 0.62 in adherence rates (i.e., approximately 15% difference in group adherence rates at post-treatment). Effect sizes for recently published social norms interventions have ranged from 0.41[24] to 0.85[58] when compared to those without social norms comparisons, and we have sufficient power to detect effects within the range of those published. The estimates of preliminary efficacy and variability of our social norms intervention that we obtain will be used to power for a future larger trial.

Randomization: At 1 month, we will randomize all patients who demonstrate adherence ≤95% to either the control group (i.e., reminders, feedback) or treatment group (i.e., reminders, feedback with social norms comparisons) using stratified block randomization with two strata and blocks of size 2 or 4 chosen randomly within each stratum. Stratification will be based on

baseline adherence (i.e., ≥ 80% or < 80%) and seizure severity (Global Assessment of Severity of Epilepsy; GASE scores 1-3 or 4-7). The PI will be blinded to study arm. The 80% criterion was selected based on our pilot data indicating that the median adherence rate for those randomized was 80%. Thus, the 95% adherence criterion is used to determine the eligibility of participants for randomization while the 80% criterion is used to balance intervention groups on baseline adherence within the randomization process. This randomization strategy will also minimize imbalance of the number of participants across groups. The randomization list will be held by an individual independent of the study to reduce any potential biases. Those who will be randomized will be notified of their randomization status within 48 hours. It is estimated that 58% of the sample will be eligible based on adherence ≤95% to be randomized to either the control group or intervention, yielding a final sample of n=80. Both groups will receive intervention for 5-months.

8.3. Data Analysis: All data analysis and management will occur at CCHMC. 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 This group will provide quality reports to audit the data routinely, provide data for safety monitoring committee reports for the biostatisticians, and cleaning of the data.

Aim 1: Examine the feasibility, accessibility, acceptability, and responsiveness of a mHealth social norms intervention to improve AED adherence for adolescents with epilepsy. H1: Adolescents with epilepsy will rate the intervention as highly feasible, easy to use, acceptable, and responsive to their needs.

Analyses Aim 1: We will examine means and standard deviations of ratings completed by adolescents on the Adapted Feasibility and Acceptability Questionnaire, Revised Website/mHealth tool Evaluation Questionnaire (WEQ), and System Usability Scale. For the Adapted Feasibility and Acceptability Questionnaire, ratings of 3-4 are considered good. The WEQ is primarily qualitative in nature and will be used during Phase 1b modifications, as well as the RCT to obtain qualitative data on the use of the social norms mHealth tool. Finally, scores on the System Usability Scale[85] ranging from 80-100 range indicate good to excellent usability.

Aim 2: Examine the preliminary efficacy of the mHealth social norms intervention on AED adherence, seizure severity, and HRQOL in adolescents with epilepsy. H2a: Participants in the treatment group will demonstrate statistically significant *improvements* in adherence with corresponding medium/large effect sizes compared to the control group at post-treatment. H2b: Greater improvements in seizure severity, HRQOL, and adherence are expected at 3-month follow-up for the treatment versus control group.

Analyses Aim 2: For the pilot RCT, adherence will be calculated using daily adherence data and collapsed for the one-month prior to treatment (baseline adherence) and the one-month following treatment (post adherence). For example, if a patient is prescribed their AED twice a day and takes 50 of their 60 doses in the month, their adherence rate would be 83.3% (total doses taken/total doses prescribed x 100%). For the follow-up period, three-month adherence will be calculated to assess sustainability of treatment effects. All analyses will be carried out with missing data assumed to be missing at random and handled via maximum likelihood estimation with auxiliary correlates[113] within Mplus (Version 8) on the full randomized sample (N=80). An ANCOVA model will be used to test the primary hypothesis that the mHealth social norms group will demonstrate significantly higher adherence rates compared to the control group at post-treatment (one-month of adherence following intervention), after controlling for

baseline adherence (1-month of adherence prior to intervention), age, sex, SES, seizure type, side effects, and cognitive/executive functioning[114] (Aim 2, H2a). When examining our secondary outcomes (i.e., seizure severity, HRQOL) and adherence at 3-month follow-up (Aim 2, H2b), the same statistical model and covariate logic employed for our primary hypothesis will be used in a longitudinal mixed model.

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 as a result. The information obtained from this study can ultimately be used to increase knowledge in the scientific community about how to improve adherence in adolescents 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. The study 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 sometimes feel uncomfortable receiving performance feedback, but based upon our previous work in Phase 1 the seriousness of such a risk is low. 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 at CCHMC will be contacted immediately to assess the situation. The study PI or their designee will provide appropriate referrals and/or intervention. Safety procedures for suicidal ideation and reports of abuse/neglect are delineated in our safety monitoring committee plan (See Appendix C). 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, and a portal created by CCHMC to receive push notifications related to their adherence feedback or social norms 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. For the individual adherence and social norms feedback reports, participants will be asked to provide a cell phone number to receive

push notifications. Adolescents' cell phone numbers will also be added into the portals maintained by Vaica and AdhereTech so that automated digital reminders can be sent to participants. This information and protection of the participant's identify will be clarified in the informed consent and assent forms.

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 adolescents with 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 C. Dr. Modi (PI) and the PI at the collaborating site, as well as 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

Participants 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. Adolescents and caregivers (i.e., only one caregiver per family) will each receive $10 for completing baseline questionnaires, $15 for completing post-treatment questionnaires and $20 for completing the 3-month follow-up assessment. If the adolescent uses the electronic monitor for the duration of the study and returns the monitor at the end of the study, they will receive an additional $25. Thus, adolescents who comply with all study procedures can be compensated $70 and caregivers can be compensated up to $45 via their ClinCard. Because we are asking current active participants to complete the new COVID-19 measure to asses for the acute effects of COVID-19, we will be compensating them an additional $5 for its completion. This will be part of the battery of questionnaires for those newly enrolled or future study visits for those enrolled, so no additional compensation will be given for its completion at those timepoints.