

Official Title of the study: **Randomized Controlled Trial of Web Based Tools to Improve Medication Continuity in Adolescents with ADHD**

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ABSTRACT:

Medication is an efficacious treatment strategy for adolescents with attention-deficit/hyperactivity disorder (ADHD) (Chan et al. 2016), however use significantly declines during adolescence when the consequences of ADHD are most severe (e.g. dropping out of school, delinquency, etc.) (Visser et al. 2014). The Unified Theory of Behavior Change (UTBC) (Fishbein et al. 2001) has been proposed as a conceptual model to explain the mechanism underlying ADHD medication adherence and to guide the development of interventions to improve the continuity of treatment (Chacko et al. 2010). The UTBC is a well-established and empirically tested model that identifies factors that influence an individual's intention to perform a behavior as well as factors that influence whether a behavior is actually carried out (Fishbein et al. 2001). Indeed, our preliminary data support the relevance of pre-intention factors and implementation factors for medication continuity among adolescents with ADHD. For example, we found that a significant majority of adolescents intentionally stop taking medicine because they question the medicine's benefits (i.e., Expectations in model). We also found that adolescents who intend to take medicine experience a variety of barriers to taking it regularly, including deficient organizational and problem solving skills, inconsistent access to timely refills, and lack of daily routines to support continuity (Brinkman et al. 2012). For example, an adolescent may repeatedly forget to take their medicine.

Customizable interventions are available to address these factors. For example, pediatrician-supervised trials on and off medicine are recommended in ADHD practice guidelines (Pliszka 2007; AAP 2011) to shape *expectations* related to benefit vs. unwanted effects of continued medicine use. However, these rarely occur in practice, leaving adolescents to conduct impromptu experiments stopping their medicine and often experiencing a negative outcome before realizing that medicine is still needed (Brinkman et al. 2012). Forgetting to take medicine can be addressed by programming regular text message reminders, which may help make medicine taking more automatic.

Currently, no interventions target medication continuity for adolescents with ADHD. Our research team is well positioned to create an intervention that addresses each of the main UTBC factors influencing the intention and implementation of regular medicine taking. With NIH funding, we have developed web-based interventions that improve the care and outcomes for young children with ADHD (Epstein et al. 2011, 2016) and improve adolescent medication continuity for other chronic conditions (Hommel et al. 2013). Such an intervention would transform care for adolescents with ADHD and help prevent the alarming fall-off in effect size from medication efficacy studies to effectiveness in real world practice caused by poor adherence.

PURPOSE OF STUDY:

The primary goal of the proposed project is to test a multi-component intervention that systematically identifies and targets aspects of the UTBC model most relevant for each adolescent with poor ADHD medication continuity. Our central hypothesis is that our tailored intervention will support ADHD medication continuity, and ultimately improve outcomes for adolescents with ADHD.

BACKGROUND:

Statement of the problem

ADHD is the most common mental health condition of childhood (Perou et al. 2013) affecting 6.4 million children aged 4-17 years in the United States (Visser et al. 2014). Children

with ADHD experience impairments across a wide range of areas of functioning including academics, social relationships, and family functioning (Wehmeier et al. 2010). Fortunately, efficacious treatments for ADHD exist. Medications, either alone or in combination with behavior therapy, reduce ADHD symptoms and some areas of impairment (MTA 1999; Chan et al. 2016) and are recommended as a first-line treatment in clinical practice guidelines (Pliszka 2007; Wolraich et al. 2011). Medication use is quite common among children with ADHD, but use plummets after age 11 even though adolescents continue to demonstrate symptoms and impairment (Visser et al. 2014; Howard et al. 2016). Moreover, those who continue to take medicine take their medications inconsistently (i.e., only 50% of days covered with medicine; Molina et al. 2009).

Developmental influences

Changes during adolescence likely contribute to the decline in medication continuity. Most teenagers expect to have a voice in decisions that concern them. Collaborative decision making between parents and children is a part of normative development that precedes full decision-making autonomy (White 1996; Wills et al. 1996). Teen involvement in medical decisions may positively impact self-efficacy, satisfaction with medical care, adherence, and, ultimately, the transition to adult health care (McCabe 1996; White 1996; Wills et al. 1996; Walker et al. 2001; Schmidt et al. 2003; Miller et al. 2014). However, many parents are afraid to give their teen with ADHD a say in decisions about medicine because they believe it helps and worry that teen goals are short sighted (Brinkman et al. 2009; Brinkman et al. 2012). Many adolescents desire to stop taking medicine because they don't believe it helps or they don't like how it makes them feel. Some teens describe feeling 'zoned out' or less social, less creative, more irritable, or experience other somatic side effects (e.g. headache, etc.) (Knipp 2006; Meaux et al. 2006; Singh et al. 2010; Brinkman et al. 2012). Moreover, many teens are given the day-to-day responsibility for medication taking, and are increasingly without the safety net of parental supervision (Brinkman et al. 2012; Brinkman et al. 2016).

Impact of poor medication continuity

As a result of these developmental changes, teens with ADHD evidence low rates of medication continuity. Unfortunately, at the same time medication continuity declines, the outcomes of ADHD become increasingly consequential. For example, adolescents with ADHD are more likely than their peers to have fewer friends, drop out of school, use tobacco and illicit drugs, interact with the juvenile justice system, be treated for sexually transmitted infections, and have teen age pregnancies (Barkley et al. 2006; Molina et al. 2009; Bussing et al. 2010). Given that medicine has large effects on adolescent performance across a variety of domains (e.g. academic tasks, social skills, etc.) (Smith et al. 1998; Evans et al. 2001; Chan et al. 2016), poor medication continuity represents a significant public health problem. Because the vast majority of adolescents receive ADHD care from pediatricians in primary care practices (Albert et al. 2017), any intervention that will address this problem must be amenable to this setting. An intervention that improves medicine continuity during the transition from family- to self-management of a teen's mental health condition would transform care and outcomes by closing the gap between medication efficacy and effectiveness in real world practice.

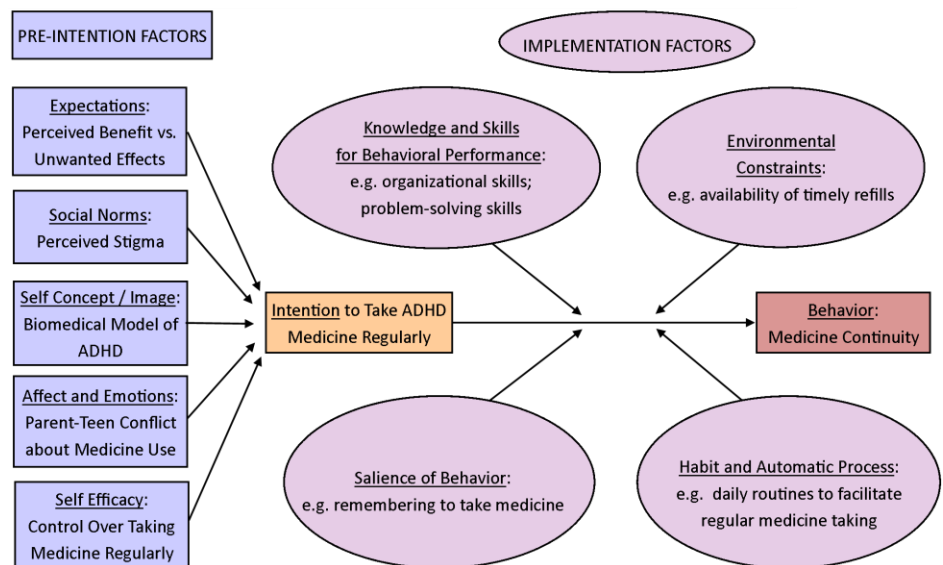
Mechanisms supporting medication continuity

Maintaining continuity of medication treatment among adolescents with ADHD is often difficult and influenced by heterogeneous factors. Indeed, different families have different needs at different times. A large body of basic behavioral science research has shown that behavioral change and maintenance of that change is best accomplished by addressing underlying mechanisms of change (i.e., beliefs about the pros and cons of the behavior, social norms and

influences, self-efficacy beliefs, and the degree to which any individual actually intends to adopt a behavior) (Armitage et al. 2000). Hundreds of studies have demonstrated that interventions must address these underlying mechanisms in order to reliably change behavior (Ajzen 1991; Jaccard et al. 1999; Fishbein et al. 2001; Rhodes et al. 2013). The UTBC (Fishbein et al. 2001) has been proposed as a conceptual model to explain the mechanism underlying ADHD medication continuity and guide the development of interventions to improve it (Chacko et al. 2010).

The UTBC identifies two processes in behavioral change (see **Figure 1**). The first process focuses on 5 determinants of an individual's willingness, intention, or decision to perform a critical behavior (see pre-intention factors on left of **Figure 1**): 1) Expectations (also called expected-values) refers to an individual's perceived advantages and disadvantages of performing the behavior. For example, in the case of taking a medication, an adolescent might believe with varying degrees of certainty that a medication will help her/him pay attention at school, but s/he may also believe that these benefits may be outweighed by other negative consequences (e.g., side effects). 2) Social Norms include two components, a) the adolescent's perceptions about what their parents think s/he should do with respect to the behavior (i.e. taking medicine), and b) the adolescent's perceptions about whether his/her peers would also approve of and/or perform the behavior. Thus, the more stigma an individual feels about taking medicine for ADHD (Pescosolido et al. 2007), the less likely it is that s/he will decide to do so. 3) Self-concept and image considerations refer to an individual's concept of one's self and whether performing the behavior is consistent with or contradicts one's self-image, rendering the behavior more or less attractive. An individual who strongly feels that ADHD is a biomedical condition that requires biomedical treatment and s/he is the type of person who always takes action to improve their health will be more likely to take medicine for ADHD than one who does not (Leslie et al. 2007); 4) Affect and emotions refers to an individual's affective and emotional reactions to behavioral performance: individuals who have a strong negative emotional reaction to taking medicine because they equate it to a battle for control with their parents will be less inclined to regularly take medicine than if one feels like their parent involves them in decisions that impact them. Adolescent-parent conflict often flows from differences of opinion about the benefit of medicine with parents worrying that adolescents are short sighted in their goals and overestimate their competence compared to objective criteria (Owens et al. 2007; Brinkman et al. 2009). Conversely, adolescent involvement in decision making (e.g. sharing opinions, negotiating with parent) has been related to higher levels of treatment regimen adherence in chronic conditions like diabetes (Miller et al. 2014). 5) Self-efficacy refers to one's beliefs that s/he can perform the behavior, and how easy/difficult it is to perform the behavior. Thus, an adolescent who believes that s/he can easily take medicine regularly within their daily routines will be more willing to do so (i.e., higher self-efficacy beliefs

Figure 1: UTBC model adapted for Medication Continuity Among Adolescents with ADHD



negative emotional reaction to taking medicine because they equate it to a battle for control with their parents will be less inclined to regularly take medicine than if one feels like their parent involves them in decisions that impact them. Adolescent-parent conflict often flows from differences of opinion about the benefit of medicine with parents worrying that adolescents are short sighted in their goals and overestimate their competence compared to objective criteria (Owens et al. 2007; Brinkman et al. 2009). Conversely, adolescent involvement in decision making (e.g. sharing opinions, negotiating with parent) has been related to higher levels of treatment regimen adherence in chronic conditions like diabetes (Miller et al. 2014). 5) Self-efficacy refers to one's beliefs that s/he can perform the behavior, and how easy/difficult it is to perform the behavior. Thus, an adolescent who believes that s/he can easily take medicine regularly within their daily routines will be more willing to do so (i.e., higher self-efficacy beliefs

will result in stronger behavioral intentions). Each of these five factors predicts variation in behavioral intentions or the decisions whether to perform specific behaviors.

The second set of four factors affect whether strong behavioral intentions are actually carried out (see implementation factors on right side of **Figure 1**). One variable pertains to the requisite knowledge and skills for behavioral performance - one may intend to take ADHD medicine regularly, but may subsequently find that s/he does not have the skills needed to take medicine every day. For example, some adolescents struggle to swallow pills. Adolescents may also lack the organizational and/or problem-solving skills needed to take medicine reliably. Another variable is the environmental constraints that may render behavioral performance difficult or impossible. For example, adolescents taking ADHD medicine are often dependent on their parent(s) to obtain medicine refills. This is often relevant because parents of adolescents with ADHD are more likely to have ADHD and/or depression (Chronis et al. 2003) which may interfere with their ability to support medication continuity by obtaining timely refills. Third, saliency of the behavior is important so that the person does not forget to enact it. Even when saliency is present, forgetting can be a challenge for adolescents with ADHD. Finally, habit and automatic processes may influence behavior. For example, by force of habit, a person who has developed a routine to help them to remember to obtain and take their medicine regularly will be more likely to sustain this behavior when competing intentions are activated and distractions are present.

We acknowledge that adolescent medication continuity is a complex phenomena and that no model can capture all of the factors and directionality that lead to medication continuity. Indeed, self-efficacy is likely influenced by past experiences managing pre-intention and implementation factors. In addition, Figure 1 fails to capture the important roles that parents and pediatricians play in supporting medication continuity. Regardless of these limitations, the UTBC conceptual model helps explain the mechanism underlying ADHD medication continuity and will help guide efforts to develop and test interventions (Chacko et al. 2010).

Pre-intention factors influencing ADHD medication continuity

We analyzed data from the Multimodal Treatment Study of Children with ADHD (MTA) to determine the prevalence of factors that impact adolescents' intentions to take medicine regularly (Brinkman et al. 2016). Twelve years after enrolling in the MTA, patients completed a survey reporting their age when they last stopped taking medicine for a month or more and their reasons for stopping. 94% of the sample (350/372) reported stopping, with a mean (SD) age of 14.2 (3.5) years when they last stopped taking medicine for ADHD. The most commonly endorsed reasons for stopping medicine related to questioning whether medicine was still needed or helped. Reasons related to side effect concerns were endorsed by a significant minority of adolescents (33-46%). The most commonly endorsed adolescent reasons for re-starting medicine related to recognition that medicine was helping at school or work (86%), with 45% of adolescents coming to realize that medicine was still needed after they had stopped taking it. For both stopping and restarting, the proportion endorsing some reasons differed by age range, with the overall pattern suggesting that parental involvement in stopping and restarting medications decreased with age. 98% of participants continued to have functional impairment after stopping medicine.

Implementation factors influencing ADHD medication continuity

We conducted focus groups with adolescents with ADHD (n=44) and parents (n=52) (Brinkman et al. 2009, 2012). Using an inductive approach to code transcripts and identify saturated themes, we elucidated a variety of barriers to medication continuity when adolescents intended to take medicine regularly. Some adolescents struggle with swallowing pills. Parental involvement in medication taking ranged from providing direct supervision, to reminders, to providing no supervision. Adolescent responsibility for medication taking increased with age and

maturity. However, many adolescents acknowledged that forgetting to take their medication was still an issue. Indeed, the organizational difficulties experienced by many adolescents with ADHD and their parents, who are at higher risk for ADHD themselves (Chronis et al. 2003), are a significant barrier to reliably obtaining refills before medicine runs out and taking medicine regularly. Moreover, parents often benefit from training on how to set goals, use behavioral contracts and rewards/consequences to encourage desired behaviors from their children with ADHD (Chronis et al. 2006), though these approaches have not been applied to ADHD medication continuity.

Intervention development requires adolescent, parent, and pediatrician participation to ensure all needs are met

We have a strong record of success conducting ADHD research in partnership with primary care practices. 10 studies conducted by Drs. Brinkman and Epstein have involved 180 practices, 616 pediatricians, and 3011 families (Epstein et al. 2007; Epstein et al. 2008; Brinkman et al. 2009; Epstein et al. 2010; Brinkman et al. 2011; Epstein et al. 2011; Brinkman et al. 2012; Brinkman et al. 2013; Brinkman et al. 2016; Brinkman et al. 2016; Epstein et al. 2016). Dr. Brinkman developed and is testing an intervention to improve adherence among 118 children with ADHD ages 6-10 years cared for by 43 pediatricians. By engaging parents in the intervention development process for this study, we learned that the Vanderbilt ADHD Rating Scales (used by pediatricians around the country to monitor response to treatment) lack salience. Parents voiced a need to be able to track specific behaviors that were important for their child. As a result, we developed this capability in the intervention. In focus groups we've conducted in preparation for the proposed project, adolescents have voiced a similar need. Teens would like to be able to track outcomes that matter most to them and depend on their report. For example, parents and teachers have a perspective on how teens get along with peers, but only the teen can say whether they feel accepted by their peers or experience stigma. Teens we met with are eager to have their voice more fully integrated in the process of treatment monitoring.

Leveraging a web-based intervention used by parents and pediatricians to efficiently conduct the proposed research and facilitate future dissemination

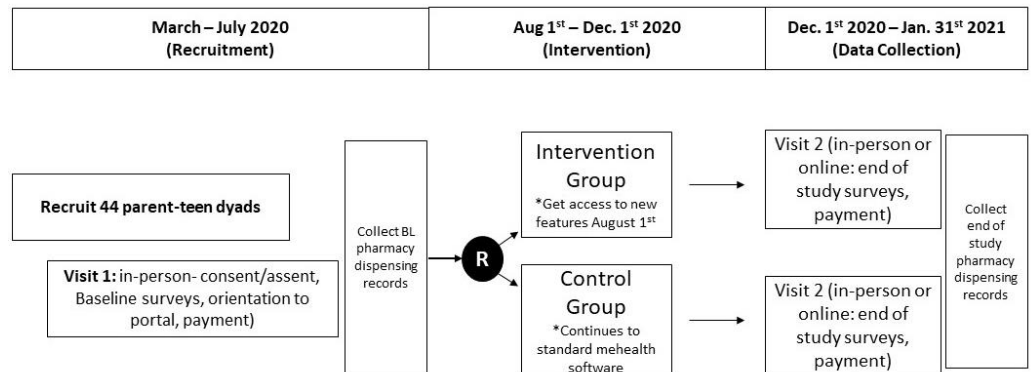
Dr. Epstein developed a web-based intervention (mehealth for ADHD) which enables community-based pediatricians to deliver higher quality ADHD care (Epstein et al. 2011) leading to children with significantly fewer ADHD symptoms (Epstein et al. 2016). Subsequently, partnerships with the American Academy of Pediatrics and American Board of Pediatrics helped spread use of the portal beyond practices that participated in research and now includes 17,412 patients cared for by 890 pediatricians in 659 practices across the US. These practices use the portal as a registry to manage their entire ADHD patient population. With pediatricians continuing to enroll patients on the portal as part of routine clinical care, opportunity exists to leverage this infrastructure to efficiently develop and test new interventions. The proposed research would fill a sizable gap as the current portal is focused exclusively on young school age children with ADHD and medication adherence has not been targeted nor improved. Specifically, while a randomized controlled trial testing the efficacy of the mehealth for ADHD web intervention demonstrated significant effects on children's treatment outcomes, there was not a significant intervention effect on medication adherence (i.e., 59% of days covered by children in the mehealth for ADHD portal group vs. 54% in the control group) (Epstein et al. 2016). Moreover, the portal is devoid of features for adolescents. In focus groups, pediatricians, parents, and adolescents have repeatedly requested such features.

STUDY DESIGN:

We will conduct a 4-month parallel group RCT among adolescents with poor medication continuity (see **Figure 2**) to test whether the intervention engages the mechanism underlying medication continuity and improves outcomes. We will recruit 44 adolescents with ADHD with poor medication continuity from Cincinnati Children’s Pediatric Primary Care Clinic (PPCC) to test the intervention. Currently, there are 230 adolescents aged 11-15 seen at PPC who are diagnosed with ADHD, taking ADHD medication, and are registered on mehealth for ADHD.

Therefore, there is a large group of adolescents from which to recruit. In preparation for research, we will assess the number of prescriptions written for ADHD medicine from their electronic medical record to ascertain basic

Figure 2:



eligibility criteria. Because the medication experiment feature is not clinically relevant for adolescents taking a non-stimulant ADHD medication, and this is a key portion of the intervention, those who are taking non-stimulant medications will not be included. At the time of enrollment, families will schedule an in-person visit during which parents and adolescents will complete baseline measures and receive training on how to use mehealth for ADHD. If families are unable to complete this visit in-person, consent and assent will be completed over the phone, measures will be sent electronically via REDCap, and study staff will conduct training on how to use mehealth for ADHD remotely (i.e. using Zoom to share screen). Before participants are randomized, we will verify the number of days covered with medicine based on dispensing data. This estimate will be used for the stratified randomization procedure. Participants will be randomized into either the intervention group or control group. The control group will continue to use the standard mehealth for ADHD software, and the intervention group will receive access to the intervention features. Because medication use varies widely during the summer months and school holidays, the intervention will begin just prior to the start of the school year to reduce variation in medication continuity based on time of year. The trial will end 4 months later. At that time, families will complete end of study measures, and pharmacy dispensing records will be obtained. The end of study measures may be completed in-person or electronically.

DURATION:

This IRB protocol covers the second phase of the study during which we will test the medication continuity tools developed in collaboration with our stakeholders during the first phase of the study. Families will be enrolled in the study for approximately 10 months.

PROCEDURES:

Research Participant Recruitment and Obtaining Informed Consent

All participants will be recruited from Cincinnati Children’s Hospital PPCC. A research assistant will initiate phone contact with PPCC patients who appear eligible based on their age,

being registered on mehealth for ADHD, and having less than 80% of days covered with ADHD medicine based on prescriptions written in the past year. Phone calls will serve to provide information about the study and answer questions. Those who express interest will complete screening questions needed to verify eligibility criteria. If they are eligible, the research assistant will schedule an in-person visit during which they will review the full consent and assent form with the parent and adolescent. After we review the content of the consent form with the parent, they will record their consent on REDCap using a study-specific consent form modeled after the eConsent demo on the REDCap Resource Center. We will also explain the study to children (in language appropriate to them; see below), and record their assent in REDCap. Following this, participants will complete their baseline surveys and receive a ClinCard to reimburse them for their study visit. If families are unable to complete this visit in-person, it will be completed remotely via phone call and/or video conferencing.

Inclusion/Exclusion Criteria

Inclusion Criteria: Participants for the study must meet all of the following criteria:

- a. Consent: The family must provide informed consent by parents or legal guardians
- b. Assent: Children must provide assent to participate in the study
- c. Ages 11-15
- d. Treated for ADHD by pediatrician
- e. First prescribed ADHD medicine more than one year prior to enrollment
- f. Have < 80% of days covered by ADHD medicine in the past year of treatment (based on pharmacy dispensing records)
- g. Filled at least one prescription for a stimulant medication in the past year

Exclusion Criteria: Participants will be excluded from the study if they meet any of the following criteria:

- a. Poor understanding level: The participant and parent cannot understand or follow instructions given in the study.
- b. Have \geq 80% of days covered by ADHD medicine in the past year of treatment (based on pharmacy dispensing records)
- c. Do not have reliable access to the internet at their home or another location.
- d. Will not permit their child to access the internet for study related activities
- e. Are not able or willing to send or receive text messages

Intervention

The intervention addresses the main UTBC factors influencing the intention and implementation of regular medicine taking. Items from standard UTBC scales (Ajzen et al. 1981) will assess the relevance of pre-intention factors and items from the validated Adolescent and Parent Medication Barriers Scales (Simons et al. 2007; Simons et al. 2010) to assess the relevance of implementation factors (see **Measurement**). After this assessment battery is collected from adolescents and parents, automated algorithms identify and recommend the specific intervention components tied to UTBC factors that are most relevant to address the needs of each adolescent/parent.

We will send weekly text message reminders to parents in the intervention group with prompts to use the new features on the mehealth for ADHD website. These messages will highlight a new intervention tool each week with a subject specific URL to take the parent

directly to the tool. The parent will receive different text message prompts depending on what tools were recommended and have been used.

We will also call parents in the intervention group to understand their experience with using the mehealth for ADHD website. The parent will be asked different questions depending on their level of engagement with the website. We will additionally ask about how their child is managing school and their ADHD symptoms. The phone call will take place as a semi-structured interview.

Intervention components targeting UTBC pre-intention factors

1. **Education** (Targeting **adolescent and parent** expectations, self-concept, affect and emotions)

The intervention delivers education about relevant topics (e.g. the etiology of ADHD; how medicine works; the importance of medication titration, how to mitigate side effects and minimize dosing regimen complexity, and how adolescents, parents, and doctors can work together to titrate medicine, conduct a trial on/off, and discourage diversion).

2. **Pediatrician supervised medication management** (Targeting **adolescent and parent** expectations, self-concept, affect and emotions).

Overview: Pediatricians can play a critical role supporting medication management and continuity of treatment, if they have the right information and teens and parents are actively engaged in the process. When teen and parent responses to the assessment battery suggest that the teen may benefit from additional titration or a trial on/off medication, the teen and parent will all be alerted to the recommendation. Adolescents and parents will be guided through a series of customized steps using program routines, called wizards. A software wizard is a user interface type that presents a sequence of dialog boxes that lead the user through a series of steps towards goal completion. Wizards will prompt patients and parents to identify, prioritize, and discuss behavioral targets to monitor during titration or trial on/off medicine.

Medication titration: Dosage adjustment and/or titration of a medicine with a different chemical ingredient will be recommended to optimize effectiveness when a teen/parent indicate they are interested in trying a new medication or dose. Parents and adolescents who express interest in changing medicine or dose will be directed to make an appointment with their pediatrician to discuss what the best option is for the family. Videos that describe different medication/treatment options will also be available for the parents and adolescents.

Pediatrician supervised trial on/off optimal dosage: A structured trial on/off medicine will be recommended when teen/parent responses to the assessment battery indicate uncertainty about whether medicine is still needed because the teen appears to be thriving. The intervention delivers training on how to conduct a high quality trial on/off medicine will include the ADHD clinical practice guideline recommendations (Pliszka 2007; AAP 2011) that differentiate these trials from the common clinical practice of stopping medication during summer or holiday breaks from school (e.g., best when there are few transitions or demands [mid school year], avoid at beginning of any school year, especially at the start of junior/senior high school, discontinue medication for 2-4 weeks, monitor target outcomes). The trial on/off medicine is designed to reduce ambivalence about medicine (i.e. document improvement among teens that still benefit) which may motivate self-directed changes to support medication continuity. Of note, trials on/off non-stimulant medication have limited utility given that atomoxetine and guanfacine take 4-6 weeks before maximal response is achieved and guanfacine can't be abruptly stopped due to risk of rebound hypertension (Froehlich et al. 2013). Accordingly, pediatricians will advise each family regarding the value of conducting an on/off trial in each situation.

Symptom & side effect monitoring: The mehealth for ADHD intervention enables the tracking of ADHD symptoms, medicine side effects, and other outcomes that are important to

adolescents and parents. In addition, adolescents and parents can construct their own measures using a structured approach with examples to ensure that adolescents and parents can translate what matters most to them into a measure that can be tracked over time. For example, an adolescent could decide to record the presence of a relevant side effect (e.g. irritability) on a daily basis. A parent could decide to track the time spent completing homework every night. Adolescents and parents can report on their chosen outcomes via an internet survey that has been optimized for completion on a mobile screen. The system provides reminders to adolescents and parents to rate targeted outcomes by cell phone text messages. At the conclusion each titration or trial on/off medicine, the pediatrician, adolescent and parents will regroup to discuss what was learned using a report generated by mehealth for ADHD to visualize the outcome data that was collected. The intervention also includes a tool that will enable parents and/or adolescents to indicate side effect(s) that are problematic for them. The tool will guide them through solutions that may mitigate the side effect(s) they are experiencing from their ADHD medication.

3. **Stigma** (Targeting **adolescent and parent** social norms)

Videos normalizing ADHD and medication taking: There are hundreds of videos available on YouTube related to ADHD (Kang et al. 2016). Some videos share information about successful people with ADHD. Other videos feature celebrities talking about how medication helps them manage ADHD. Yet other videos, like TED talks, feature adolescents and adults discussing how they have made sense of ADHD and have been successful managing ADHD symptoms. Other videos discourage diversion of ADHD medicine. The intervention includes links to videos that may help adolescents normalize ADHD and medication taking and discourage diversion.

Intervention components targeting UTBC implementation factors

4. **Organizational interventions: Refill reminders; visual cues, pill taking reminders** (Targeting **adolescent and parent** habits and automatic processing, and environmental constraints)

The portal enables parents and/or adolescents to schedule reminders for when to request a refill from the pediatrician's office. Adolescents and parents will also be oriented to strategies such as use of visual cues embedded within their daily routine to take medicine (e.g. putting pill bottle next to toothbrush, etc.). Adolescents will be able to schedule daily text message reminders to take medicine.

5. **Monitoring medication taking** (Targeting **adolescent, parent, and pediatrician** salience)

After receiving their text message reminders to take their medication, adolescents will be sent a second text message asking if the dosage was taken with response options of Yes/No. This will enable tracking of medication to inform a feedback loop for self-monitoring. Tracking results will be displayed graphically to make it easy to assess trends over time relative to interventions that have been implemented to improve medication continuity.

Measures to characterize the sample

1. Demographics: Adolescents, parents, and pediatricians will report on age and race/ethnicity. Parents will also report on child insurance status, and their own level of education and mental health history.
2. Technology Use Survey: Adolescents and parents will complete this 30-item phone survey from the Pew Research Center's Internet & American Life Project (PewResearchCenter 2011). Items query respondents about use of various types of devices (e.g. desktop, tablet, smartphone, etc.), internet connections (e.g. cable modem, etc.), and activities (e.g. internet browsing, emailing, texting, downloading apps, etc.).

3. Vanderbilt ADHD Parent Rating Scale: (VADPRS) (Wolraich et al. 2003) has subscales for Inattention and Hyperactivity/Impulsivity. In addition, a symptom count score can be derived for DSM-IV items and includes a subscale to assess parents' perceptions of youth school and social functioning.
4. ADHD Self-Report Scale: The ASRS is a self-report measure of the 18 DSM ADHD symptoms (Kessler et al., 2005). Items reflect symptoms of inattention and hyperactivity-impulsivity, and in this study all items will be rated by teens on a 4-point scale (0 = never; 3 = very often) consistent with the parent- and teacher-completed VADRS.
5. Pittsburgh Side Effects Rating Scale: (Pelham et al. 1993) is a 13-item measure that allows adolescents and parents to report whether ADHD medicine side effects were none, mild, moderate, or severe.
6. The Columbia Impairment Rating Scale (CIS) Parent and Child Versions (Appendix Q & R): The Columbia Impairment Rating Scale (CIS) assesses impairment in behavioral, emotional, interpersonal, and task-related functioning. Behavioral functioning includes problems with behavior at home and school; emotional impairment involves feeling nervous or sad; interpersonal impairment taps problems in relationships with peers, siblings, parents, and other adults; and task-related functioning includes problems with schoolwork and involvement in leisure activities. Parents reported how much of a problem each of these areas of impairment was for their child on 13 items using a 7-point scale ("No problem" to "Extreme problem"). The CIS has shown high internal consistency, excellent test-retest reliability, and good validity when correlated with a clinician's score on the Children's Global Assessment Scale.
7. COVID-19 Adolescent Symptom and Psychological Experience Questionnaire (CASPE): The COVID-19 Adolescent Symptom and Psychological Experience (Ladouceur, 2020) is an adolescent and parent report of the psychological impacts of the pandemic. Items assess negative affect and changes in caregiver employment or income due to COVID-19.
8. Remote and In-Person Learning during COVID-19: This is a 25-item measure that allows parents to report on adolescent engagement in remote, blended, and in-person learning during COVID-19. Two items were used from the Home Adjustment to COVID-19 Scale (HACS) (Becker et al., 2020) to assess parent confidence and challenges experienced when assisting with remote learning.

Outcome measures

9. Fidelity to intended use of intervention components: For each adolescent and parent, we will calculate the proportion of intervention components completed relative to the components that were recommended by the portal based on adolescent/parent responses to the assessment battery. For intervention components that are used once (e.g. trial on/off medicine), we will identify a portal data element to characterize intervention component completion. For intervention components that are used more than once (e.g. refill reminders, pill taking reminders, etc.), we will define "intended use" of the feature as use for at least 2 months since research suggests that, on average, it takes 2 months to develop a new habit (Lally et al. 2010). Mehealth for ADHD will capture and report on these data elements to characterize fidelity to the intended use of intervention components for each adolescent and parent.
10. Pre-intention factors of UTBC influencing medication continuity (Appendix G & H): Our measurement strategy for the adolescent and parent pre-intention factors closely follow well-developed procedures (Ajzen et al. 1981). We will use standard scales that have been used in hundreds of previous studies using the UTBC and closely related basic science theories. For example, an item to assess social norms would be "Most of the

people who are important to me think I should take ADHD medicine regularly.” Responses are on a 7-point scale from strongly agree (+3) to strongly disagree (-3). The internal consistency of items within each construct is good ($0.7 \leq \alpha \leq 0.9$) (Steele et al. 2005; Bentley et al. 2009; Cornelio et al. 2009; Boyko et al. 2011). For this study, we will assess pre-intention factors (i.e. expectations, social norms, self-concept/image, affect and emotions, and self-efficacy) framed around the behavior of “taking ADHD medicine regularly” following published methods (Francis et al. 2004) and informed by our prior qualitative research (Brinkman et al. 2009, 2012).

11. Behavioral Intentions (Appendix I & J): Teen and parent intention for teen to take ADHD medicine regularly will be measured using the standard measure of intention from the UTBC (Ajzen and Fishbein, 1981).
12. Implementation factors of UTBC influencing medication continuity (Appendix K & L): These factors will be measured using the Adolescent and Parent Medication Barriers Scales (AMBS and PMBS) (Simons et al. 2007; Simons et al. 2010). Adolescents and parents respond using a 5-point Likert-like scale from “strongly disagree” to “strongly agree” to report perceived barriers to medication taking. Both the adolescent scale (17-items) and parent scale (16-items) have strong internal consistency for total score and the four factor-analytically derived subscales: ‘Disease frustration/adolescent issues’, ‘Regimen adaptation/cognitive’, ‘Ingestion issues’, and ‘Parent reminder’. For criterion-related validity, adolescents classified as non-adherent had significantly higher barrier scores than those classified as adherent. In prospective validation studies, the adolescent-perceived barriers of ‘Disease frustration/adolescent issues’ and parent-perceived barriers of ‘Regimen adaptation/cognitive issues’ were associated with poorer adherence to medication taking (Simons et al. 2010).
13. Medication Continuity: We will calculate the percentage of days covered with medicine based pharmacy dispensing records and verified by parent report of ADHD service use using the reliable Services for Children & Adolescents – Parent Interview (Eaton Hoagwood et al. 2004). This measures ADHD service use, including office visits and medication use. We have successfully obtained pharmacy dispensing records via parental permission for 95% (155/164) of subjects across 2 studies (R01 MH074770, K23 MH083027) (Brinkman et al. 2013; Brinkman et al. 2016). Pharmacy dispensing records provide an objective, unobtrusive, reliable measure that is a well-accepted proxy for medication consumption (Steiner et al. 1997) that was significantly correlated with the more expensive and invasive Medication Event Monitoring System (MEMSCap™) which uses a microprocessor in the medication container cap to record the day and time of each vial opening (Farley et al. 2003).
14. Medication Diversion: Self-report of giving away, trading, or selling ADHD medicine to someone for whom it was not prescribed will be collected via a confidential web-based survey used in past population-based studies of middle/high school students. (Boyd et al. 2007; McCabe et al. 2011a).
15. Client Satisfaction Questionnaire (CSQ) (Attkisson et al. 1982) is an 8-item unidimensional measure of client satisfaction with services. Psychometric properties, operating characteristics, and coefficient alpha (.93) are very strong for this measure which we will collect from adolescents and parents.
16. Decision Making Involvement Scale (DMIS) (Miller et al., 2012): is a 30-item scale to measure adolescent involvement in a decision. The five subscales are: “Child Seek” (child asks for an opinion or information from parent), “Child Express” (child expresses an opinion or information to parent), “Parent Seek” (parent expresses advice or opinion to child), “Parent Express” (parent expresses advice or opinion to child), and

“Joint/Options” (negotiation or brainstorming between parent and child). We will collect this measure from adolescents and parents.

DATA ANALYSIS

Hypothesis testing:

Each hypothesis examines part of the mechanism underpinning intervention impact on medication continuity.

Hypothesis #1: *Adolescents will use greater than 80% of relevant intervention components.* For each subject in the intervention group, we will calculate the proportion of **recommended** intervention components that were utilized by the subject during the study. The mean and 95% confidence interval (CI) will be computed to give a range estimate of the fidelity measure. To evaluate our hypothesis, we will utilize the computed CI to determine if 80% or greater is a plausible value, such that if the CI includes a value of 80% or greater we will reject the null hypothesis. We will also examine the temporal distribution of use for each of the recommended components.

Hypothesis #2: *Use of the intervention components will be related to improvements in the targeted UTBC factors.* Using a generalized linear model, we will test whether the intervention addressed the UTBC factors (i.e., pre-intention factor scales and ABMS/PBMS total and subscale scores). Model predictors will include a fixed effect indicator of time point (baseline or end of study). A significant effect of time point in the expected direction would indicate UTBC factor improvement.

Hypothesis #3: *Medication continuity will be higher in the intervention group compared to the control group.* We will compare the percentage of days covered with medicine using a two-sample t-test.

Hypothesis #4: *Pre-post changes in UTBC factors will be related to increases in medication continuity.* We will calculate the change score for each relevant UTBC factor (end of study minus baseline) and the change score for medication continuity (percentage of days covered at end of study minus percentage of days covered in the 12 months prior to study). We will model the association between change in UTBC factor scores (independent variable) with change in medication continuity (dependent variable) using generalized linear mixed model. A significant effect of change in UTBC factor scores (beta coefficient) in the expected direction would indicate changes in UTBC factor scores were associated with medication continuity improvement.

Exploratory analyses:

We will conduct descriptive analyses to characterize rates of diversion at baseline and at the end of study using a McNemar's test to see if rates differ. We will summarize responses to the client satisfaction questionnaire descriptively as this may facilitate future dissemination.

Power and Sample Size:

The study would require a sample size of 18 for each group (i.e. a total sample size of 36), to achieve a power of 80% and a level of significance of .05 (two sided), to detect a difference in means between the intervention and the control groups of 15.7% (i.e. 66.2% vs. 50.5%) on the percentage of days covered with medicine assuming a pooled standard deviation of 16.5. Due to the low intra-class correlations observed in previous studies of ADHD medication continuity (ICC = 0; Brinkman et al. 2018), the analyses will not account for the nesting of patients within physicians. We will recruit 44 patients to ensure that 36 are retained at the end of the study. A retention rate of 80% (36/44) is conservative in light of the 12-month retention rate of 92% achieved by Dr. Hommel in his current trial. We will use a stratified blocked randomization procedure to ensure baseline medication continuity is evenly distributed in both arms.

Scientific Rigor:

The RCT is a rigorous design to test efficacy of our intervention. We will explicitly address whether the intervention engages the mechanism underlying medication continuity and therefore warrants further testing in a future larger trial. Our preliminary data strongly supports the importance of the problem, intervention targets identified, and the feasibility of the approach in our hands.

Randomizing at the patient level, introduces a risk of contamination because it is possible that physicians will have encounters with patients assigned to both intervention and control arms. We are taking several steps to mitigate this risk. First, we have designed the software so that intervention components can be selectively “turned on” for patients allocated to the intervention group. Second, most intervention components will be used directly by patients and parents. For example, teens might choose to receive daily text message reminders to take their medicine. Parents might choose to receive text message reminders to obtain refills. Teens and/or parents might watch videos about ADHD, medication, stigma, etc. Again, these features won’t be “turned on” for patients in the control group. Some intervention components, like medication experiments promote interactions between patient, parent, and pediatrician. Pediatricians will have awareness of these features and receive training on how to interact with families to discuss what they learned from conducting an experiment. That said, it is unlikely that families allocated to the control group will conduct such experiments if they don’t have access to this intervention component in the mehealth for ADHD software.

FACILITIES

Cincinnati Children’s Hospital is the performance site for this study.

POTENTIAL BENEFITS

Although we cannot guarantee a benefit to any individual participating pediatrician, adolescent, or parent, the intervention components we propose to integrate into the ADHD web portal are theory- and evidence-based strategies with significant support from the research and clinical literature. Thus, families randomized to receive the intervention have the potential to benefit from state-of-the-art treatment. Benefits of the study outweigh any potential risks because our interventions are likely to improve care and outcomes for children who receive them.

POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES, AND PRECAUTIONS

There is minimal risk to the participants in this study other than a potential for invasion of privacy. Because confidential information about study participants will be available to study staff, procedures to safeguard the confidentiality of this information are required. As an NIH funded study, a Certificate of Confidentiality protects the privacy of research subjects by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents. Additionally, several safeguards will be put in place. All data collected on pediatricians, adolescents, and parents will be assigned a unique code that will be linked to identifying information. The master coding sheet that will link the information will be kept in the study coordinator’s office under lock and key. In addition to assuring confidentiality of the research data, it is also critical that the confidentiality of the patient’s clinical information is protected in mehealth for ADHD. The HIPAA regulations and their application to this product will be clearly defined to ensure compliance within their guidelines. Mehealth for ADHD was designed with a procedure for encrypting and storing the

data in such a manner to only allow pediatricians to view identifiable data. This design employs a key-based encryption structure. This method does require extra security information to be maintained by the parties who are encrypting the data. For example, parties needing access to the data are assigned a "key" that is used to encrypt and decrypt the data in addition to a user ID. Such a key will be maintained by the PI and kept under lock and key. Implementation of additional methodologies to keep the confidential information off the server will be implemented including such methodology as ensuring the CCHMC server is secure (i.e., firewalled).

Data from this study may be submitted to the National Institute of Mental Health (NIMH) that allows researchers studying mental health and substance use to collect and share deidentified information with each other. If participants consent to have their information shared in the data repository, all personal information about research participants such as name, address, and phone number will be removed and replaced with a code number. Participants may decide at any point that they do not want to share their information to the NIMH data repository. If a family consents to have their data shared, the information required to create their deidentified code number will be collected during the phone screen by a member of the research team.

PROTECTION OF VULNERABLE POPULATION

Because children are being invited to participate in the study, the following procedures will be followed to avoid issues related to coercion or undue influence. First, study staff will review the assent form with participating children, in language appropriate for their intellectual functioning and developmental levels, and ask whether or not the child agrees to participate. Similarly, they will be told that they can opt not to participate or answer any questions which they do not want to answer at any time. This will be re-iterated whenever necessary.

RISK/BENEFIT ANALYSIS

The risks to participants are minimal and unlikely, largely stemming from the possibility of loss of confidentiality. We have instituted provisions to minimize this risk and will assure participants of the voluntariness of their participation and their right to withdraw participation at any time. We will also take appropriate steps to safeguard confidentiality. We would suggest that this study falls under the "Minimal Risk" category.

ALTERNATIVES

Participation in the present study is completely voluntary. The alternative to participation in the study is to choose not to participate in the study.

DATA SAFETY & MONITORING

Physicians, adolescents, and parents who agree to participate and are randomized to the intervention group will receive access to a version of the mehealth for ADHD that has been enhanced with new intervention components. Given that the risks to participants are minimal, there does not appear to be the need for an external monitoring board. Rather, the Drs. Brinkman (PI) and Epstein (co-I) will assume primary responsibility for the ongoing monitoring of the data and safety of the study, and will provide reports of this with annual renewal application to the IRB and annual progress report to the sponsor. Both are experts in ADHD management, ADHD research, and have experience conducting practice-based research such as that proposed in this application. Dr. Brinkman has medical expertise related to pharmacotherapy of

children with ADHD to address study-related medical issues. All research staff will complete education in the protection of human research subjects.

Drs. Brinkman and Epstein will continuously evaluate the project's performance, safety, and need to stop. Performance will be monitored by examining subject recruitment, comparison with targeted recruitment retention, protocol adherence, and quality of data collection procedures. This will primarily be accomplished in weekly staff meetings attended by Drs. Brinkman and Epstein.

Drs. Brinkman and Epstein will be available at all times to address any safety issues. Any serious adverse events will be determined by Drs. Brinkman and Epstein and reported to the IRB within 24 hours, specifying the nature of the event and outcome, if related to the study and if anticipated or not. If a serious adverse event as a result of participation in the study occurs, recruitment will be immediately discontinued until the serious adverse event has been reported to the IRB and the IRB has deemed it appropriate for the study to continue.

COST OF PARTICIPATION

There will be no costs to the subject for participating in this study.

PAYMENT FOR PARTICIPATION

Each parent/adolescent dyad will be compensated \$200 for the visit at the beginning of the study, and \$100 for the visit and surveys at the end of the study for a total of \$300 throughout the intervention. All payments will be made at the end of each visit to the parent. ClinCards will be used for all payments.

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