Title: Open-Label Trial of personalized medication experiments to inform decisions about future ADHD medication use

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ABSTRACT:

Medication is an efficacious treatment strategy for adolescents with attention-deficit/hyperactivity disorder (ADHD);[1] however, use significantly declines during adolescence when the consequences of ADHD are most severe (e.g. dropping out of school, delinquency, etc.).[2] The Unified Theory of Behavior Change (UTBC)[3] 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.[4] 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.[3] 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.[5] For example, an adolescent may repeatedly forget to take their medicine.

Pediatrician-supervised trials on and off medicine are recommended in ADHD practice guidelines[6-8] to shape *expectations* related to benefit vs. unwanted effects of continued medicine use. However, these rarely occur in practice,[9] leaving adolescents and parents[10] to conduct impromptu experiments stopping their medicine and often experiencing a negative outcome before realizing that medicine is still needed.[5] Interventions to support such trials have been described,[11] but not tested. In previous research (IRB #2020-0236), our research team created an intervention that addresses each of the main UTBC factors influencing the intention and implementation of regular medicine taking. The current study will test an intervention component to support structured medication experiments to inform decisions about future medication use.

PURPOSE OF STUDY:

The primary goal of the proposed project is to test personalized medication experiments to inform decisions about future medication use. Our central hypothesis is that our intervention will lead to within subject increases in adolescent involvement in decision making and decreases in uncertainty about future medication use. We view this open label trial as a pilot study to test the feasibility, acceptability, and preliminary efficacy of the medication experiment intervention and therefore warrants further testing in a future larger trial.

BACKGROUND:

Statement of the problem

ADHD is the most common mental health condition of childhood[12] affecting 6.4 million children aged 4-17 years in the United States.[2] Children with ADHD experience impairments across a wide range of areas of functioning including academics, social relationships, and family functioning.[13] Fortunately, efficacious treatments for ADHD exist. Medications, either alone or in combination with behavior therapy, reduce ADHD symptoms and some areas of impairment[1,

[14] and are recommended as a first-line treatment in clinical practice guidelines.[6, 7, 15] Medication use is quite common among children with ADHD, but use plummets after age 11 even though adolescents continue to demonstrate symptoms and impairment.[2, 16] Moreover, those who continue to take medicine take their medications inconsistently (i.e., only 50% of days covered with medicine[17]).

Developmental influences

Changes during adolescence likley contribute to the decline in medication continuity. Most adolescents 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.[18, 19] Adolescent involvement in medical decisions may positively impact self-efficacy, satisfaction with medical care, adherence, and, ultimately, the transition to adult health care.[18-23] However, many parents are afraid to give their adolescent with ADHD a say in decisions about medicine because they believe it helps and worry that adolescent goals are short sighted.[5, 24] 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 adolescents describe feeling 'zoned out' or less social, less creative, more irritable, or experience other somatic side effects (e.g. headache, etc.).[5, 25-27] Moreover, many adolescents are given the day-to-day responsibility for medication taking, and are increasingly without the safety net of parental supervision.[5, 28]

Impact of poor medication continuity

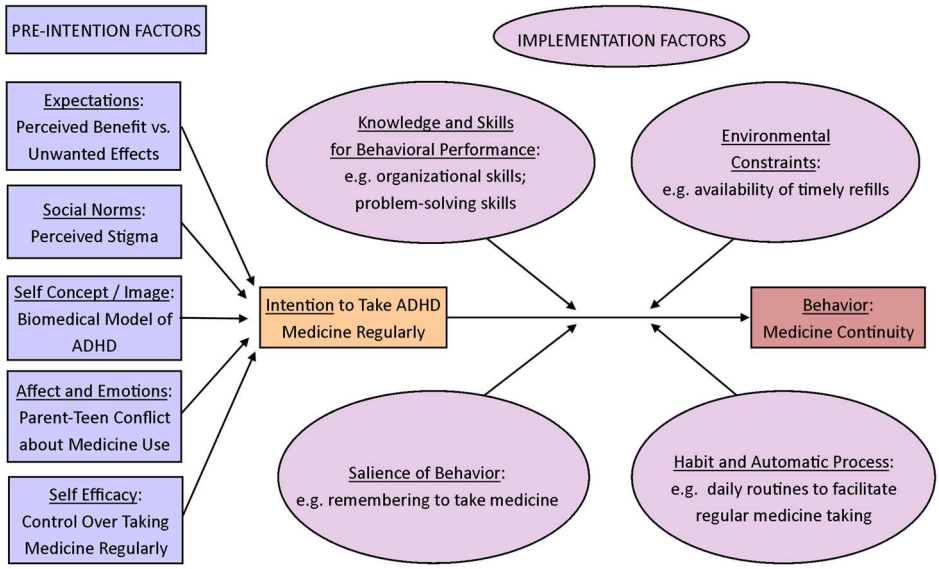
As a result of these developmental changes, adolescents with ADHD evidence low rates of medication continuity. Unfortunately, at the same time medication continuity declines, the outcomes of ADHD become increasingly consequential. For example, adolescents with ADHD are more likely than their peers to 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.[17, 29, 30] Given that medicine has large effects on adolescent performance across a variety of domains (e.g. academic tasks, social skills, etc.),[1, 31, 32] poor medication continuity represents a significant public health problem. Because the vast majority of adolescents receive ADHD care from pediatricians in primary care practices[33] 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 adolescent'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).[34] Hundreds of studies have demonstrated that interventions must address these underlying mechanisms in order to reliably change behavior.[3, 35-37] The UTBC[3] has been proposed as a conceptual model to explain the mechanism underlying ADHD medication continuity and guide the development of interventions to improve it.[4]

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[38] 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;[39] 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.[24, 40] 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.[23] 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.

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



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[41] which may interfere with their ability to support medication continuity by obtaining timely refills. Third, salience of the behavior is important so that the person does not forget to enact it. Even when salience 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 was used in our past research to guide efforts to develop interventions.

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.[28] 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).[10, 42] 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,[41] 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,[43] though these approaches have not been applied to ADHD medication continuity.

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

By engaging parents in the intervention development process, 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 conducted, adolescents voiced a similar need. Adolescents 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 adolescents get along with peers, but only the adolescent can say whether they feel accepted by their peers or experience stigma. Adolescents we met with were 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

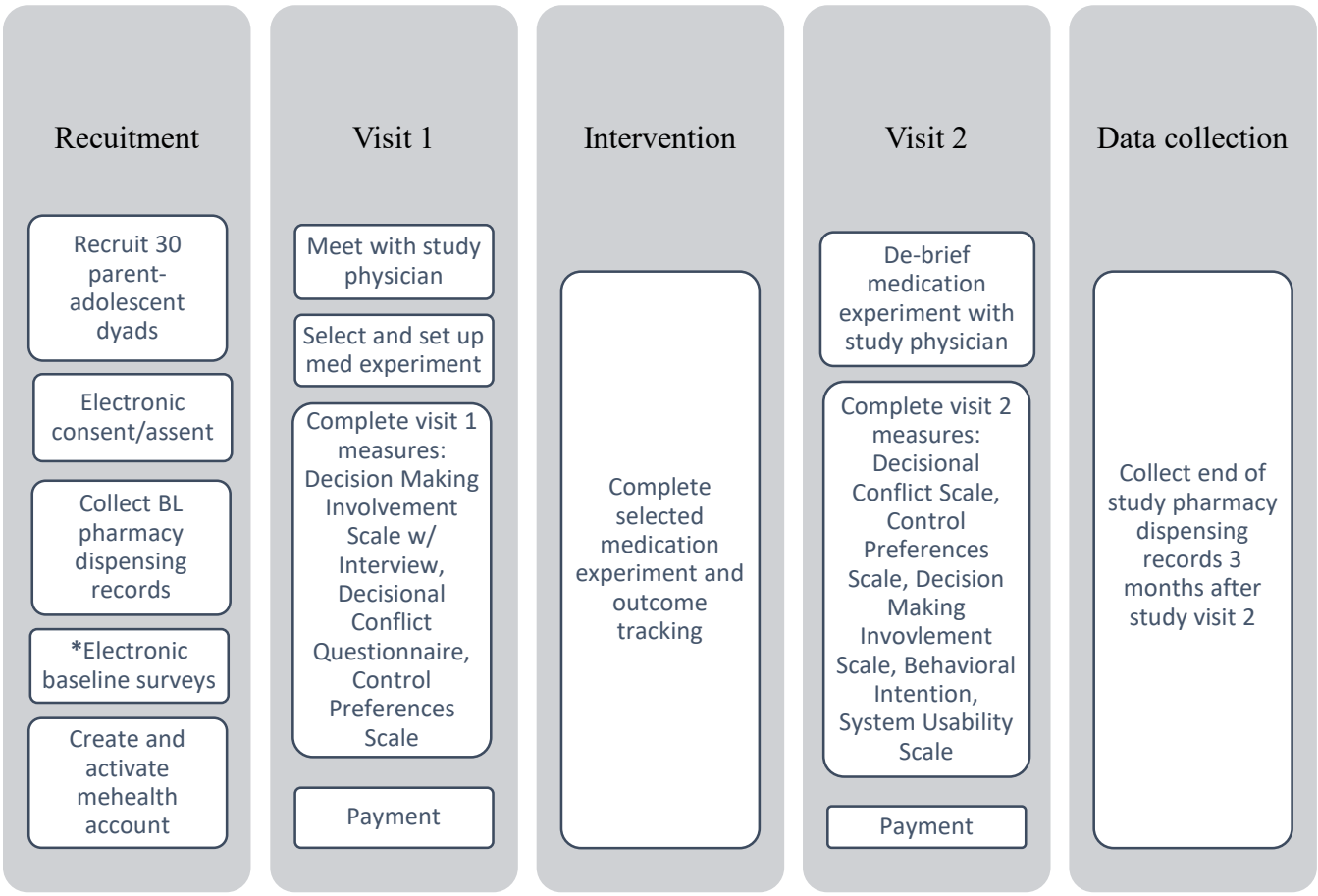
Dr. Epstein developed a web-based intervention (mehealth for ADHD) which enables community-based pediatricians to deliver higher quality ADHD care[44] leading to children with significantly fewer ADHD symptoms.[45] Subsequently, partnerships with the American Academy of Pediatrics and American Board of Pediatrics helped spread use of the portal beyond practices that participated in research and now includes 60,801 patients cared for by 2,153 pediatricians in 886 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 infrastucture 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).[45] 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 pilot, single-arm, open-label trial of the medication experiment feature among 30 adolescents experiencing uncertainty about continued medicine use (see **Figure 2**). Because the medication experiment feature is not clinically relevant for adolescents taking a non-stimulant ADHD medication, they will be excluded. At the time of enrollment, families will complete baseline measures electronically and schedule an in-person visit. We will verify the medication prescribed and the number of days covered with medicine in the past year using

dispensing data. During the visit, parents and adolescents will receive training on how to use mehealth for ADHD and will choose one of the five medication experiments to complete together and track the effects for the desired amount of time. Once dyads have completed the medication experiment, they will complete a follow-up study visit to review the results from the experiment, discuss feasibility of the software, and complete end of study measures.

Figure 2.



*Electronic baseline surveys: Demographics, Health-Care Literacy Scale, Vanderbilt Scale/ADHD Self-report, Columbia Impairment Scale, Pittsburgh Side-Effect Rating Scale, Pre-Intention Factors, Medication Barriers, Behavioral Intention, Conflict Behavior Questionnaire, and (adolescents only) Medication Diversion

DURATION:

This IRB protocol covers the phase of the study during which we will test the medication experiment feature developed in collaboration with our stakeholders during the first phase of the study. Families can customize the start and end date as well as the amount of time they track effects in the medication experiment. Thus, families could be enrolled in the study for up to 4-

months. We expect that all 30 dyads will be recruited and complete the study participation over the course of one year.

PROCEDURES:

Research Participant Recruitment and Obtaining Informed Consent

All participants will be recruited from Cincinnati Children's Hospital. We will advertise the study to CCHMC employees via flyers and emails to recruit their eligible adolescents to participate. Parents will be able to contact the research team to receive additional information. Those who express interest will complete screening questions needed to verify eligibility criteria. If they are eligible, the research assistant will review the full electronic consent and assent forms with the parent and adolescent via phone call. 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 adolescents (in language appropriate to them; see below), and document their assent in REDCap. Once 30 dyads have been consented and enrolled, parents that filled out the interest form that were never called by the study team will be sent a blind carbon copy email via REDCap that explains that the target participant goal has been met and they will be put on a waitlist in the case of participant attrition. They will also be contacted at study completion to inform them that the study is no longer recruiting.

Inclusion/Exclusion Criteria

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

a. Consent: A parent or legal guardian must provide written informed consent
b. Assent: Adolescents must provide written 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. Filled at least one prescription for a stimulant medication in the past year
g. Uncertainty about continued ADHD medication use
h. Only one child per household can participate in the study. For families who have more than one child who is potentially eligible, they may decide which of their children would be the best fit for the study.

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

a. Do not have reliable access to the internet at their home or another location.
b. Will not permit their child to access the internet for study related activities.
c. Are not able or willing to send or receive text messages.

Intervention

At baseline we will collect items from standard UTBC scales[46] to assess the relevance of pre-intention factors and the strength of their intention to take/give medicine, and items from the validated Adolescent and Parent Medication Barriers Scales[47, 48] to assess the relevance of

implementation factors (see **Measurement**). Once baseline surveys have been completed, we will create a meHealth account for the dyad and schedule an in-person study visit at the Center for ADHD. Study visits will not be scheduled if there is missing survey data as parent and adolescent engagement providing responses electronically is critical to success of completing the medication experiment which involves tracking outcomes.. The study physician will meet with the dyad to gather history and better understand their past experience with medication. The study physician and research assistant will collect the DMIS introductory interview to identify the most recent ADHD medication decision made by family (e.g. stop for summer, resume for school year, adjust dosage, change medication, etc.) and then each will complete the decision making involvement scale independently.

During our development process, we identified the following types of experiments that are often relevant:

1. Make no changes. Track current state: continue to take medication as it is currently prescribed.
2. Take medication on non-school days. Track effects: If not currently taking medication on non-school days, start taking medication on those days and track the effects.
3. Stop taking medication on non-school days. Track effects. If currently taking medication on non-school days, stop taking medication on those days and track the effects.
4. Do a formal trial off of medication. Take current medication as currently prescribed for 2 weeks while tracking, then stop taking medication for 2-4 weeks while continuing to track.
5. Change dose or change medication. Consider a different medication or different dose of current medication in consultation with study doctor. Track the effects.

The study physician will discuss these options with the dyad, they will then select the medication experiment they would like to complete. Next, the study physician and research assistant will use the meHealth software with the dyad to identify, prioritize, and discuss behavioral targets to monitor during the experiment.

Subsequently, the adolescent and parent will be asked to independently indicate the option they expect to prefer after the experiment ends (continue [medication regimen from experiment], resume previous medication/dosage, conduct another experiment, return to pediatrician to adjust dosage or change medication, other), their certainty about the decision, and their preferred role in decision-making (see Measures).

The study physician will confirm that there are no cardiac risk factors (adolescent history of heart disease, family history of sudden death in children, hypertrophic cardiomyopathy, long QT syndrome) that might preclude the use of stimulant medications and complete a brief physical exam. The adolescent's pediatrician likely assessed this prior to starting stimulant medication.

All medication experiments involving a change in medication regimen will involve tracking outcomes for 2 weeks on their current regimen and a minimum of 2 weeks after making a change. We will partner with dyads to select the order, typically starting with current regimen. In randomized controlled trials of ADHD medication discontinuation, relapse is typically noticed

within 2 weeks.[49] Hence, we are confident that most participants won't require repeated cycles of treatment and non-treatment as classically described in the N-of-1 trial literature.[50] Dyads will be able to reach the study team between visits if untoward effects (e.g. relapse of symptoms/impairment, side effects, etc.) convince them to end the experiment early and/or resume their previous regimen. We will follow best practices for medication experiments recommended in ADHD clinical practice guidelines[6, 7] These include conducting when there are few transitions or demands (i.e. mid school year), and avoiding at beginning of any school year, especially at the start of middle school or high school. The trial on/off medicine is designed to reduce ambivalence about medicine (i.e. document improvement among adolescents who still benefit) which may motivate self-directed changes to support medication continuity.

Symptom & side effect monitoring: The mehealth for ADHD software 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. It is important to note that parents and adolescents may track different outcomes. This reflects differences in what's important to them as well as differences in what they are best positioned to report on. For example, only adolescents can report on how the medicine makes them feel. Only parents can report on what they observe. 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. The research assistant and study physician will also be available by phone to answer questions and/or address concerns that arise.

We will monitor on-going medication experiments for each dyad and will be available if questions or concerns arise. We will additionally reach out to parents if we identify any difficulties using the website.

At the conclusion of the medication experiment, the research assistant will schedule an in-person study visit at the Center for ADHD. The study physician, adolescent and parents will discuss what was learned using a report generated by mehealth for ADHD to visualize the outcome data that was collected. Subsequently, the adolescent and parent will be asked to independently indicate their preference for what to do next (continue [medication regimen from experiment], resume previous medication/dosage, conduct another experiment, return to pediatrician to adjust dosage or change medication, other), and their preferred role in decision-making. The study physician will then facilitate a discussion to resolve any differences between adolescent and parent preferences and come to a consensus. The parent will receive a study summary document to share with their child's pediatrician so s/he is aware of what was learned and can use this to guide future management decisions. The adolescent and parent will report this decision, their certainty about the decision, their preferred role in decision-making, their involvement in the process of making this decision, and their intentions about taking/giving medicine. We will also ask the parent and adolescent about the usability the medication experiment software (see Measures).

Measurement Strategy: Aggregation of individual trials to estimate a population level treatment effect isn't needed given the strong evidence of stimulant effectiveness among adolescents.[1] Rather, it is important to ascertain whether the use of medication experiments helps adolescents and parents work together to resolve uncertainty about future use of medicine. We will describe the type and number of medication experiments conducted as well as the personal outcomes selected for tracking. We will examine process outcomes like the decision-making involvement, comfort with the decision made, and whether the decision was implemented.

Measures to characterize the sample on demographic, ADHD, and psychosocial factors

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. Digital Health Care Literacy Scale: Adolescents and parents will complete this 3-item measure with responses on a 5 point strongly disagree to strongly agree scale: 1. I can use applications/programs (such as Zoom) on my cell phone, computer, or another electronic device on my own (without asking for help from someone else), 2. I can set up a video chat using my cell phone, computer, or another electronic device on my own (without asking for help from someone else), 3. I can solve or figure out how to solve basic technical issues on my own (without asking for help from someone else). Total score with range of 0 to 12 is created by summing the score of individual items, with higher scores indicating higher literacy. The scale has excellent reliability (Cronbach α=.90) and discriminates between those with and without access to and/or use of technology.[51]
3. Vanderbilt ADHD Parent Rating Scale: (VADPRS)[52] has subscales for Inattention and Hyperactivity/Impulsivity. In addition, a symptom count score can be derived for DSM-IV items.
4. ADHD Self-Report Scale: The ASRS is a self-report measure of the 18 DSM ADHD symptoms.[53] Items reflect symptoms of inattention and hyperactivity-impulsivity, and in this study, all items will be rated by adolescents on a 4-point scale (0 = never; 3 = very often) consistent with the parent-completed VADPRS.
5. Pittsburgh Side Effects Rating Scale: The Pittsburgh Side Effects Rating Scale[54] 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 (See Compendium of Measures) 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. For each area of impairment, parents report how much of a problem for "your child" and adolescents self-report how much of a problem for "you". There are 13 items with 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. Conflict Behavior Questionnaire (CBQ), parent and adolescent versions. Each will complete the CBQ, which is a 20-item scale that assesses the relationship between parent and adolescent.[57] The scale measures conflict and negative communication between parents and adolescents through dissatisfaction with the other's behavior and evaluations of the interaction between the two members. This instrument has demonstrated high reliability (α = .9 - .95).[57]
8. Pre-intention factors of UTBC influencing medication continuity (See Compendium of Measures): Our measurement strategy for the adolescent and parent pre-intention factors closely follows well-developed procedures.[46] 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 ($0.7 \leq \text{alpha} \leq 0.9$).[58-61] 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[62] and informed by our prior qualitative research.[10, 42]
9. Implementation factors of UTBC influencing medication continuity (See Compendium of Measures):): These factors will be measured using the Adolescent and Parent Medication Barriers Scales (AMBS and PMBS).[47, 48] Adolescents and parents respond using a 5-point Likert-type scale with ratings 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.[48]
10. Past Year Medication Continuity: We will calculate the percentage of days covered with medicine based pharmacy dispensing records. We have successfully obtained pharmacy dispensing records via parental permission for 95% (155/164) of subjects across 2 studies (R01 MH074770, K23 MH083027).[63, 64] Pharmacy dispensing records provide an objective, unobtrusive, reliable measure that is a well-accepted proxy for medication consumption[65] 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.[66]
11. Medication Diversion: **Adolescent** 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.[67, 68]

Decision-Making Preferences—The Control Preferences Scale[69] assesses the degree of control an individual wants to assume when decisions are being made about medical treatment. The Control Preferences Scale will be modified so that adolescents and parents choose preferred control options that range from the adolescent solely making the decisions regarding choice of medication experiment, to the adolescent making the decisions jointly with the parent, to the parent solely making the decisions.

Outcome Measures

12. 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 use the Decision-Making Involvement interview guide to collect this measure at study visit 1 and the stand-alone version to collect it study visit 2.
13. Certainty about the decision will be measured using the Decisional Conflict Scale (DCS): The DCS[70] has an initial question to ascertain the option that has been selected. Options presented will be: continue [medication regimen from experiment], resume previous medication/dosage, conduct another experiment, return to pediatrician to adjust dosage or change medication, other [write in]. The DCS then has 16 questions that are divided into five subscales: informed subscale, values clarity subscale, support subscale, uncertainty subscale, and an effective decision subscale. The informed subscale measures how informed participants feel about the benefits and risks of the decision. The values clarity subscale measures a participant's feelings about personal values for benefits and risks/side effects. The support subscale measures perceived levels of support during decision-making. The uncertainty subscale measures a participant's level of certainty about the best choice to make. The effective decision subscale measures the satisfaction with the decision made. The total DCS score equally weighs all five subscales. Responses to each question are reported on a 5-point Likert scale (0 = strongly agree to 4 = strongly disagree). The total DCS scores are calculated by summing item scores and then converting the scores to a 0-100 scale, where 0 implies no decisional conflict and 100 implies extremely high decisional conflict. Scores <25, 25 to 37.5, >37.5 indicate low, moderate and high decisional conflict, respectively. Scores 25 and higher reflect clinically significant decision conflict.
14. Behavioral Intention questions that will assess the adolescent and parent intention to take/give ADHD medicine regularly will be measured using the standard measure of intention from the UTBC.[46] Responses are on a 7-point scale from strongly agree (+3) to strongly disagree (-3) that assess intention to take medicine for ADHD on weekdays, weekends, and school vacations.
15. System Usability Scale (SUS)[71] is a validated 10-item unidimensional scale with response options on a 5-point agreement scale which results in a score from 0 to 100, with higher scores indicating greater usability.

Implementation of decision: 3 months after study visit 2, we will obtain pharmacy dispensing records to ascertain whether their joint decision was implemented. If medication was continued, we will calculate the percentage of days covered.

DATA ANALYSIS

We will conduct descriptive analyses to summarize measures that characterize the sample in terms of demographic, ADHD, and psychosocial factors, the experiments selected, and decisions made, as well as feasibility and usability data. In order to determine overall feasibility and usability of our pilot intervention, we will compare retention, participation, and usability ratings to a priori criteria based on previous research (i.e., retention ≥ 80%, participation ≥ 80%, usability ≥ 70),[72] using Chi-square tests.

Power and Sample Size

We selected a target sample size of 30 to exceed the recommended sample size (n = 20) for a pilot trial designed to inform a larger efficacy trial with 80% power to detect a medium effect.[73] Of note, we aren't powering the study to examine differences in outcomes by experiment type. Paired-samples t-tests will be used to calculate the change in DMIS,DCS, and behavioral intentions for all adolescents and parents, and for medication continuity among the subset who choose to continue medication after completing their experiment. Cohen's d will be calculated to estimate effect size for each pre- to post-outcome and interpreted as small (.20), medium (.50), and large (.80).[74]

Hypothesis testing

We will test the following hypotheses:

1. From pre to post, within-subject report on DMIS subscales "child express" will increase and "parent seek" will increase.
    a. Paired sample t-test
2. From pre to post, within-subject DCS will decrease.
    a. Paired sample t-test
3. Higher post-DMIS joint/decision scores will be reported by dyads who differ on initial preferences following the experiment compared to those who don't.
    a. Two sample t-test
4. Higher post-child express scores will be reported by adolescents who want to make the decision alone compared to those who prefer to share decision or have parent make decision.
    a. Two-sample t-test
5. Adolescent-parent conflict as measured at baseline by the CBQ will be positively associated with discordance in independent preferences following the medication experiment.
    a. Biserial correlation coefficient
6. The difference between the adolescent's intention to take ADHD medication and the parent's intention to give ADHD will decrease from pre to post.
    a. Linear mixed model

Scientific Rigor:

An open label trial is an appropriate design to test the feasibility, acceptability, and preliminary efficacy of the medication experiment intervention 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.

FACILITIES

Cincinnati Children's Hospital Center for ADHD is the performance site for this study.

POTENTIAL BENEFITS

Although we cannot guarantee a benefit to any individual participating adolescent or parent, medication experiments are recommended in clinical practice guidelines to help resolve uncertainty about continued medication use. Benefits of the study outweigh any potential risks because this intervention will likely improve care.

POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES, AND PRECAUTIONS

There is minimal risk to the participants in this study. For dyads who select a medication experiment involving not taking medicine for some period of time, it is possible the adolescent could experience more ADHD symptoms than usual and/or a decline in functioning. Indeed, adolescents often experience such effects when conducting impromptu experiments without physician supervision.[75] For dyads who select a medication experiment involving taking medication on additional days (e.g., non-school days) or trying a different medication or dosage, it is possible the adolescent could experience side effects which s/he may or may not have experienced in the past. Both of these scenarios are the reason why clinical practice guidelines recommend that medication experiments are personalized, structured, and physician supervised. Dyads will be able to reach the study team between visits with any concerns. Medication experiments will end early if needed.

Because confidential information about study participants will be available to study staff, procedures to safeguard the confidentiality of this information are required. Several safeguards will be put in place. Electronic data will be protected by username and password requirements. All data collected on 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 are 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 confidential information off the server will be implemented including such methodology as ensuring the CCHMC server is secure (i.e., firewalled).

PROTECTION OF VULNERABLE POPULATION

Because adolescent 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 adolescents, in language appropriate for their intellectual functioning and developmental levels, and ask whether or not the adolescent 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 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

Adolescents and parents who agree to 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, Dr. Brinkman (PI) will assume primary responsibility for the ongoing monitoring of the data and safety of the study, and will provide reports of this with the annual renewal application to the IRB and annual progress report to the sponsor. Dr. Brinkman is an expert in ADHD management and ADHD research, and has experience conducting 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.

Dr. Brinkman 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.

Dr. Brinkman will be available at all times to address any safety issues. Any serious adverse events will be determined by Dr. Brinkman 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.

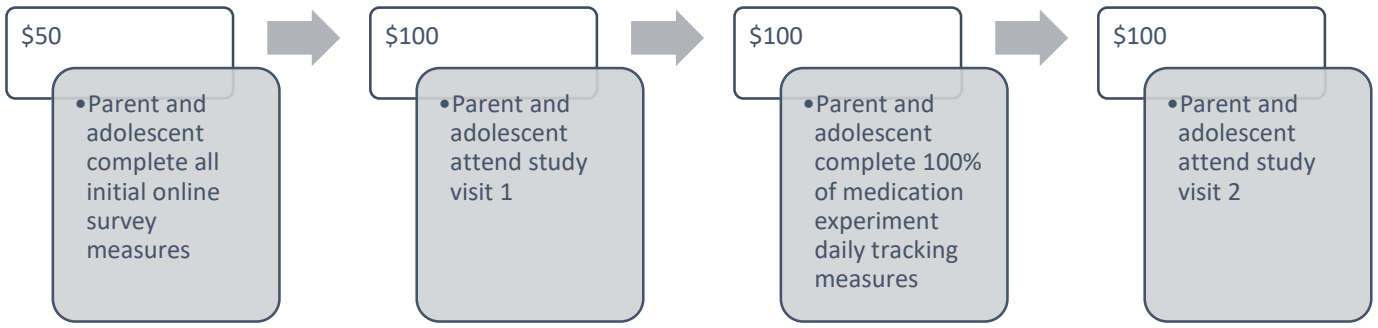
COST OF PARTICIPATION

There will be no costs to the subject for participating in this study. The study physician will provide prescriptions, as needed, during trial participation, but participants will be responsible for obtaining ADHD medication from their pharmacy as they do for typical clinical care.

PAYMENT FOR PARTICIPATION

Each parent/adolescent dyad will be compensated $50 for survey completion and $100 for completing each study visit. They will additionally receive up to $100 for time spent submitting data during the medication experiment . This will be pro-rated based on the % of days with complete data reported over days expected. For example, if the medication experiment lasts for 6 weeks and both parent and adolescent entered data for 34 out of the 42 days, they would receive 80.9% of $100 = $80.90. Therefore the maximum total compensation throughout the study is $350.

Figure 3



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