Title: Pilot Trial of Contingency Management for Long-Term Cannabis Abstinence

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PARTNERS HUMAN RESEARCH COMMITTEE

DETAILED PROTOCOL: Contingency Management for Six Months of Cannabis Abstinence among Adolescents
Protocol #: 2018P001848
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I. BACKGROUND AND SIGNIFICANCE

A. Cannabis use is common among adolescents, and will likely become even more prevalent with legalization of recreational cannabis. Cannabis is currently the most commonly used illicit substance among adolescents in the United States and is one of the only substances with steadily increasing prevalence estimates. In fact, rates of adolescent cannabis use now surpass those of cigarettes by almost two-fold[1] and rates of use are approaching those of alcohol.[2] Recent estimates suggest that approximately 15% of 12 to 17 year olds and 52% of 18 to 25 year olds have ever tried cannabis,[2] with the rates of experimental use significantly increasing over the course of high school (approximately 14% of 8th graders, 31% of 10th graders, 45% of 12th graders[1]). Patterns of regular use are also prevalent among youth, with 6% of high school students reporting daily use and 28% reporting monthly use.[1-2]

These increasing prevalence estimates may be, in part, due to the cultural context in which adolescent cannabis use occurs. There has been an overall decrease in perceived harm of cannabis use,[1] which has likely contributed to an increase in social and legal permissiveness for recreational use as well as increased acceptability and application of medicinal cannabis.[3] Massachusetts, for example, voted in favor of creating a legal commercial market for recreational cannabis in 2016, and dispensaries are slated to open any day. As many of the products sold in dispensaries are specifically marketed toward teenagers, it is probable that youth rates of use will increase. Further, there has been an increase in the availability of more potent cannabis strains, which are nearly 25 times stronger than varieties available previously.[4-5]

The more prevalent usage of a more potent drug in an era of swelling cannabis acceptance is a significant public health concern, to the extent that there are adverse sequelae from chronic cannabis exposure. A growing body of research supports the notion that cannabis may be addictive. The lifetime risk for cannabis dependence is approximately 9%, and nearly 17% when use is initiated during teenage years.[6] Although these cumulative dependence estimates are lower for cannabis than for other substances of abuse, the rate of transition from non-problematic to problematic cannabis use may occur faster than for drugs such as nicotine and alcohol.[6] Therefore, it is not surprising that use of cannabis during adolescence is associated with several short- and long-term problems. For instance, cannabis intoxication has been associated with an increased risk for motor vehicle accidents.[7-8] Additionally, use between the ages of 14 and 21 years is associated with later difficulties in the domains of education, employment, income as well as relationship and life satisfaction.[9-10]

B. The developing adolescent brain is most vulnerable to harmful effects from cannabis. Regular cannabis exposure during adolescence may cause greater adverse effects than later exposure due to ongoing neuromaturation occurring well into the third decade of life. Gray matter in areas underlying higher order cognition is last to mature, and increased myelination contributing to white matter development continues through at least the late 20s. Cannabis use is thought to affect normal neuromaturation via effects of tetrahydrocannabinol (THC) on endocannabinoid-guided neuromaturation and selective synaptic pruning during adolescence. Exposure to synthetic cannabinoids or THC during adolescence but not later in life is associated with cognitive impairments that are linked with biomarkers of aberrant neurodevelopment, including shorter dendrites and reduced spine densities in the hippocampus. Epidemiologic studies have also reported associations between earlier cannabis onset and poor neurocognition as well as abnormalities in brain activation patterns.[for a review see 11]

C. More research is needed on the relationships between neuropsychological functioning and cannabis use. Available reports have shown that adolescence may be a unique developmental window during which

cannabis exerts its most profound impact on neurocognitive functioning. Even after taking into account multiple potential confounds, those who initiate before 18 years tend to show more pronounced impairments in visual attention,[12] visual search efficiency,[13] episodic memory,[14-15] and executive functioning[16-19] as well as possible declines in intellectual functioning.[20] For example, only early age of initiation (before age 16) was predictive of impaired reaction times on a visual scanning task, above and beyond the effects of current age, THC plasma levels and cumulative lifetime cannabis exposure as compared to late onset users who were not different from controls.[12] Similarly, Solowij and colleagues[15] found that earlier age of cannabis onset was associated with poorer learning, retention and retrieval of novel verbal information even after adjusting for the frequency and amount of cannabis exposure. Further, the relationship between early cannabis use and neurocognitive concerns may also be accompanied by unique patterns of brain activity: earlier onset chronic cannabis users made more errors on a behavioral inhibition task and showed more focal activation of the middle anterior cingulate cortex than late onset chronic users.[17] These apparent neuropsychological differences among individuals with earlier cannabis debut may yield important functional implications as early age of initiation is also associated with up to a four-fold greater risk of cannabis dependence within the first two years of use.[21]

The persistence of cognitive deficits with abstinence has become an important area of inquiry in the last few years, with the goal of understanding the time course of early cognitive changes associated with intoxication and elucidate which cognitive impairments may be persistent.[22-24] In a non-randomized trial, Hanson and colleagues found remittance of memory deficits after three weeks of abstinence among adolescent cannabis users compared to non-users. A second study, which was designed to evaluate changes in cognitive performance among adolescents enrolled in a randomized, placebo-controlled trial of *N*-acetylcysteine for cannabis cessation, showed improvement in verbal memory and psychomotor speed in those who were abstinent for four or eight weeks compared to those who continued to smoke. More recently, our group found that one month of cannabis abstinence was associated with improvements in verbal learning but not attention compared to adolescent cannabis users who continued to smoke.[25] These studies provide preliminary evidence that abstinence is associated with improved neurocognitive function. However, several critical questions cannot be addressed in one-month abstinence paradigms. First, it is impossible to interpret the role of cannabis in affecting domains that did not improve more among abstainers compared to non-abstainers. Deficits may recover slower in young users due to neurodevelopmental vulnerabilities, or may represent permanent adverse effects of regular use in adolescence or a risk factor for use. A longer-term abstinence trial is necessary to tease apart whether detectable deficits at one month resolve with continued sobriety or are non-modifiable. Second, only longer abstinence trials are well positioned to determine whether the cognitive improvements measured in the laboratory translate to improved academic functioning. Addressing this gap is essential to public health messaging.

D. Rationale for Proposed Research. This proposal addresses a critical first question: is an adaptation of the one-month contingency management paradigm currently employed in our ongoing study (Protocol #: 2015P000076) effective in engendering six months of cannabis abstinence? Demonstrated feasibility and efficacy of the six-month paradigm will lay the foundation to subsequently test, in a fully powered randomized trial, whether cognition and academic functioning improves when adolescents stop using cannabis.

Currently, no studies have evaluated an incentive-based abstinence intervention beyond one month among non-treatment seeking adolescents. The long-term goal of this line of research will address critically important clinical questions of the impact of cannabis use, and particularly the potential beneficial effect of long-term cannabis abstinence, on learning/cognition and, more importantly, real-world academic functioning in adolescents. That is, to understand whether six months of abstinence results in an improvement in cognitive performance among adolescents who use cannabis regularly. This is a highly relevant question, as the perception among adolescents and often their parents/guardians, is that cannabis use does not impact their ability to learn and perform in school. It has the potential to have profound impact on our understanding of the clinical effect of cannabis on cognition in young people as well on policy, given the rapidly shifting political landscape on cannabis use in the US that will no doubt have a strong impact on prevalence and frequency of adolescent cannabis use, regardless of age restrictions on purchase.

This study is a critically important first-of-its-kind investigation of the potential research utility of using contingency management to examine long-term changes in cannabis use with six months of abstinence. These pilot data will inform a later trial which will focus on testing the longitudinal relationships between adolescent cognition and cannabis use, questions of high and growing public health significance given adolescents' increased access to cannabis with legalization.

II. SPECIFIC AIMS

This pilot study will:

Phase 0

Aim 1: Evaluate the acceptability and feasibility of a contingency management intervention for six months of biochemically verified cannabis abstinence in adolescents who use cannabis at least once per week and who are not seeking treatment.

Aim 2: Compare the initial efficacy of two different, non-randomized, contingency management intervention payment schedules (high vs low) to determine which produces more consistent rates of long-term abstinence.

Phase 1

Aim 1: Collect preliminary data on whether six months of cannabis abstinence is associated with improvement in cognitive functioning among frequent adolescent cannabis users

III. SUBJECT SELECTION

Inclusion Criteria:

1. Male and female adolescents who are between the ages of 13 and 20 (inclusive);
2. Average use of cannabis at least 1 time per week during the 3 months prior to study enrollment;
3. Cannabis use reported within 7 days of study enrollment;
4. Willing to stop using marijuana for 6 months;
5. No immediate plan to discontinue cannabis use;
6. Have a parent or legal guardian who is competent and willing to provide written informed consent for the active study phase (if under the age of 18);
7. Competent and willing to provide written informed assent for the active study phase (if under the age of 18);
8. Competent and willing to provide written informed consent (if age 18 or older);
9. Able to communicate in English language;
10. Have a parent/guardian who can communicate in English language;
11. Able to commit to 26 study visits in approximately 6 months;
12. Able to safely participate in the protocol and appropriate for outpatient level of care, in the opinion of the investigator.
13. No severe developmental delays (including, but not limited to, Autism Spectrum Disorder, Intellectual Disability, and Down Syndrome).

IV. SUBJECT ENROLLMENT

We aim to enroll 10 participants in the Phase 0 (pilot) period of the study and 20 participants in the Phase 1 period of the study.

Screening

- **Adolescents Recruited and Enrolled from The Epiphany School and Millis, Medford, Walpole, Westford, and Cambridge Public Schools: Passive Consent for School-Wide Screening.** Given the history of low response rate of studies requiring students to return parent permission forms (which limits the number of students who can be involved in the project and threatens the ability to generalize the results, thus limiting the usefulness of our research results), initial screening will largely occur as

part of a separate IRB protocol (Protocol #2015P000076) and directly at local, participating schools with passive parental consent for screening. However, active parent consent and participant assent will be required to enroll in the intervention component of the study. Potential participants will be identified through an ongoing screening process that is occurring through an already approved IRB protocol (PI: Randi M. Schuster, Protocol #2015P000076). A brief overview of the school screening procedures from our other protocol (Protocol #2015P000076), which will serve as a recruitment pipeline for the current study, is outlined below. The school-wide assessment will serve the purpose of characterizing the demographics and general behavioral profile of the schools attended by the participants. Participants will be recruited by MGH study staff from the MGH Center for Addiction Medicine and not by any district and/or school personnel. Recruitment will occur through an opt-out procedure conducted solely by MGH staff. Specifically, at the request of MGH staff, the participating school will contact all parents/guardians of 5th through 12th grade students in the school's preferred method (e.g., through reverse 9-11 calls, emails, mass mailings) indicating that MGH study staff will be distributing and collecting a very brief and de-identified questionnaire during a designated time at school. Parents and guardians will be told that they can freely withdraw their child from participating in the school-wide assessment phase without any penalty or consequence to the child, including any impact on school or educational activities and that parental written consent must be provided to MGH staff for active phase study participation. Parents and legal guardians will be informed that this is not a study or program of the respective school district, including a program of the specific school. School personnel will not be involved in administrating or operating the study in any capacity, including answering student and/or parent or legal guardian inquiries regarding the study. Parents and legal guardians will be free to contact the principal investigator of this study at MGH directly at any time if they have questions about the school-wide assessment or the specific items included on the questionnaire.

- **Adolescents Recruited and Enrolled from the Community: Waived Parental Consent for Telephone Screening.** Potential participants will be recruited via online advertisements, community flyers (see recruitment materials), and databases of participants from other lab protocols who have given explicit consent to be re-contacted for new studies. Among participants who are determined eligible through the telephone screening, under the age of 18, and interested in participating in the study, parent/legal guardian contact information will be collected to obtain informed consent for the active study phase. No active study procedures will be conducted with potential participants prior to obtaining written parent/guardian informed consent and adolescent assent for those under the age of 18 or written consent for those 18 years of age or older.

  A waiver of written consent for telephone screening only is requested and is justified given the following:

  - **The proposed research involves no more than minimal risk to participants.** During telephone screening, we will provide details about the study and ask potential participants if they have any questions or concerns about the study protocol. We will also ask participants basic demographic information as well as brief questions related to frequency and recency of cannabis use to determine eligibility. These questions are indistinguishable from questions asked during standard school substance use assessments. This telephone screener is anticipated to take no more than 10 minutes and participants are free to refuse to answer any questions. They will be told that all information will be kept strictly confidential and answers to telephone screening questions will be stored separately from any identifying information. If participants are interested in the study and are eligible, we will collect parent/guardian contact information so that we can obtain written parental consent for study enrollment. No study procedures will occur before written parental consent is obtained (parental consent if under the age of 18). We will also obtain written adolescent assent (if under the age of 18) or consent (if 18 years of age or older) at the baseline visit, prior to the initiation of any study procedures, during which time we will review the study in detail.

- **The waiver of consent for telephone screening will not adversely affect the rights and welfare of subjects.** The waiver of parental consent for telephone screening only will not adversely impact an adolescent's access to or the nature of any ongoing health services or primary care in any way nor adversely affect his/her rights or welfare. The study will be detailed to potential participants before any telephone screening questions are asked of them, giving them a chance to decline telephone screening if they are not interested in the study. They are also free to refuse to answer any telephone screening questions that make them feel uncomfortable. They will be clearly told that written parental consent and adolescent assent will be required for enrollment in the active study phase and that answers to phone-based questions are for telephone screening purposes only.
- **The research could not practicably be carried out with the waiver or alteration.** This study could not be practicably carried out without a waiver of consent for telephone screening for adolescents under the age of 18 due to the burden that would be imposed on parents/guardians of potential participants that are not yet even known to be eligible for and interested in study participation. This study utilizes a brief, de-identified telephone screen to assess whether the potential participant is interested in and eligible for the study. Telephone screening questions are similar to questions asked in standard school substance use assessments. In our experience, the consent process generally takes approximately 30 minutes, while the brief telephone screener should only take about 10 minutes or less for most participants. Requiring consent for telephone screening would thus dramatically increase parent/guardian burden, and in many cases, this imposed burden would be unnecessary because it is not guaranteed that their child is interested in or eligible for the study. Due to this increased parent/guardian burden, we expect that requiring consent for telephone screening would greatly reduce enrollment and compromise the representativeness of the sample. Therefore, we are proposing to seek written consent only for potential participants who we know are interested in and eligible for the study. It is for these reasons that our study requires a waiver of consent for participant telephone screening for adolescents under the age of 18.
- **Participants and parents/guardians will be provided with additional pertinent information after participation.** Prior to the first study visit, written parental consent will be obtained for participants under the age of 18 and parents/guardians will be provided with copies of the consent form which will fully detail the study protocol as well as any associated risks and benefits. They will be given contact information of key study staff if they would like more information. Similarly, study participants will be given a copy of the signed parental consent/study assent form.
- **The research involves no more than minimal risk to the privacy of the participants.** This research involves no more than minimal risk to the privacy of participants. During the telephone screening, only basic demographics and information to determine eligibility will be collected. The protocol fully details our plan to protect any identifying information from improper use and disclosure.

Active Study Phase

- **Adolescents Recruited and Enrolled from The Epiphany School and Millis, Medford, Walpole, Westford, and Cambridge Public Schools: Written Parental Consent and Student Assent.** Students who expressed interest in participating in the active study phase will be contacted via telephone and/or email by MGH study staff directly to describe the study, and discuss their interest in and understanding of the proposed protocol. MGH staff will send home an informed consent form containing our contact information for their parent or legal guardian, to read, consider and sign. Parents can electronically sign the consent form and send the document back to study staff if they would prefer. This option will only be available if this is preferred by parents; the opportunity to meet with study staff in person or over the phone will be made available to all parents. Parents may reach out to MGH study staff with any questions or concerns. The initial study visit will be coordinated with the student over the phone and/or via email and he/she will be told that the signed parental consent form must be received from his/her parent/guardian prior to the first visit or the student must bring the signed parental consent form to the first visit. The active phase study procedures will not begin for any participant under the age

of 18 until the parental consent form is obtained. Within the consent form is a description of collection of saliva samples for genetic analysis; parents can decline consent for DNA without penalty on participation for the rest of the project. During the initial study visit, informed assent will be obtained from the student by a trained member of the study staff prior to administering any study procedures. As in the parental consent form, students will indicate on the assent form whether they permit collection and analysis of genetic samples. All participants will be given the opportunity to ask questions to a doctoral-level member of the study staff during the assent process. Contact information of key MGH study staff will be provided and participants (and parents/guardians) will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All participants will be provided with a copy of their signed parental consent and student assent forms.

Students who are interested in participating and are over 18 years old will be contacted by a member of study staff, who will coordinate the initial study visit. At the time of such visit, informed consent will be obtained by a trained member of the study staff prior to administering any study procedures. Within the consent form is a description of collection of saliva samples for genetic analysis; participants can decline consent for DNA without penalty on participation for the rest of the project. All participants will be given the opportunity to ask questions to a doctoral-level member of study staff during the consent process. Contact information of key study staff will be provided and participants will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All eligible participants will be provided with a copy of their signed consent form.

Upon study enrollment to Phase 0, all participants will be assigned to either a high ($1,235) or low ($910) contingency management payment schedule in order to collect data that informs us on the level of payment most likely to make long-term abstinence feasible and reliably attainable (about 80% abstinence).

- **Adolescents Recruited and Enrolled from the Community Under 18 Years of Age: Written Parental Consent and Student Assent.** Parent/guardian contact information will be collected from potential participants who expressed interest in participating in the active study phase, who were found to be eligible on the telephone screen, and who are under the age of 18. Parents/guardians will be contacted directly by MGH staff. MGH staff will send an informed consent form directly to parents/guardians of potential participants under the age of 18 to read, consider, and sign. Within the consent form is a description of collection of saliva samples for genetic analysis; parent/guardians can decline consent for DNA collection without penalty on participation for the rest of the project. Along with the consent form, MGH staff will send parents/guardians contact information if a parent/guardian wants to discuss any aspects of the consent form. Parents/guardians have the option to sign the consent form in person, or electronically via Adobe System. Adobe System's digital signature feature is a secure and commonly used method of obtaining signatures electronically. The option to meet with study staff in person or over the phone will be made available to all parents/guardians. Parents/guardians may reach out to MGH study staff with any questions or concerns at any time prior to or after signing the consent form. The initial study visit will be coordinated with the participant over the phone and/or via email and he/she will be told that the signed parental consent form must be received from his/her parent/guardian prior to the first visit or the participant must bring the signed parental consent form to the first visit. The active study phase will not begin for any participant under the age of 18 until the parental consent form is obtained.

  During the initial study visit, informed assent will be obtained from the participant by a trained member of the study staff prior to administering any study procedures. As in the parental consent form, participants will indicate on the assent form whether they permit collection and analysis of genetic samples. All participants will be given the opportunity to ask questions to a doctoral-level member of the study staff during the assent process. Contact information of key MGH study staff will be provided and participants (and parents/guardians) will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All participants as well as their

parents/guardians will be provided with a copy of their signed parental consent and adolescent assent forms.

Potential Participants 18 Years of Age or Older: Potential participants who are interested in participating and are 18 years of age or older will work directly with MGH staff following completion of the telephone screen to coordinate the initial study visit. At the time of such visit, informed consent will be obtained by a trained member of the study staff prior to administering any study procedures. Within the consent form is a description of collection of saliva samples for genetic analysis; participants can decline consent for DNA collection without penalty on participation for the rest of the project. All participants will be given the opportunity to ask questions to a doctoral-level member of the study staff during the consent process. Contact information of key study staff will be provided and participants will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All eligible participants will be provided with a copy of their signed consent form.

Upon study enrollment to Phase 0, all participants will be assigned to either a high ($1,235) or low ($910) contingency management payment schedule in order to collect data that informs us on the level of payment most likely to make long-term abstinence feasible and reliably attainable (about 80% abstinence).

Participant Withdrawal (All Participants)
Participation is completely voluntary and participants may stop being in the study at any time or decide not to join the study. Similarly, parents/guardians of participants younger than 18 may withdraw their child from the study at any time or decide not to allow their child to participate in the active study phase. If a participant or parent/guardian decides not to participate, they will not be penalized in any way, and will not lose any benefits to which they are otherwise entitled.

Confidentiality (All Participants)
All phases and aspects of this project will be conducted according to the Declaration of Helsinki and will comply with HIPAA regulations. The sponsors of this research will be the only individuals who will have access to data on individuals that are stripped of all unique identifiers according to HIPAA guidelines. School staff and personnel will not have access to or receive any individual data. A Certificate of Confidentiality from the National Institutes of Health has also been obtained for this study.

Since it is required for eligibility that written informed consent from a parent/guardian be obtained for participants under the age of 18, parents/guardians will be aware through reading the informed consent form that this study is recruiting only cannabis-using adolescents. Participants will be made aware during the telephone screening process that the consent form may broadly reveal their cannabis use history to their parent/guardian. Participants under the age of 18 who do not agree to have us send an informed consent form to their parent/guardian will be deemed ineligible, as parental consent is required for eligibility and enrollment into the study. The only information a parent/guardian will be exposed to is the fact that their child uses cannabis. All further information regarding nature of cannabis use (such as frequency or amount), or any other information collected throughout the study, will be kept strictly confidential and will follow the confidentiality guidelines outlined in the Confidentiality and Privacy section of the protocol (section VII).

V. STUDY PROCEDURES

Telephone Screening

Adolescents Recruited and Enrolled from The Epiphany School and Millis, Medford, Walpole, Westford, and Cambridge Public Schools: Passive Consent for School-Wide Screening (Phase I). Screening will take place both on site at the participating schools (as part of Protocol #2015P000076), and confirmed over the phone. Data will be collected during the screening to determine eligibility in the study; this data will include general demographic items as well as basic questions related to health behavior such as frequency and recency of cannabis and alcohol use. All students who are not withdrawn from this study phase by their parents/guardians and who wish to complete the questionnaire will also complete a separate form where they indicate their interest in being contacted for the active study phase and provide their contact information. MGH

study staff will collect all school-wide questionnaires and contact information forms as well as the incomplete forms from uninterested students. The contact information form and the brief questionnaire will be immediately separated to protect individual confidentiality. Questionnaires will then be reviewed only by MGH study staff and all cannabis-using students who indicated a willingness to be contacted will be considered potentially eligible for the active study phase, pending receipt of written parental consent and student assent (see below). A screening log that includes a non-identifying subject ID, the date of screening, and enrollment decision or status (see below) will be kept for all individuals screened.

- **Adolescents Recruited and Enrolled from the Community: Waived Parental Consent for Telephone Screening:** In response to community advertisements, potential participants will call the laboratory to inquire about details of the study and complete a brief telephone questionnaire that will include general demographic items as well as basic questions related to health behavior such as frequency and recency of cannabis and alcohol use. Eligible and interested participants under the age of 18 will be asked for parent/guardian contact information to coordinate obtaining written parental informed consent. Eligible and interested participants age 18 and older will schedule their baseline study visit with MGH staff and informed consent will be obtained directly from these participants at their baseline visit. A screening log that includes a non-identifying subject ID, the date of screening, eligibility status, and enrollment decision/status will be kept for all individuals screened.

Active Study Phase (The Epiphany School and Millis, Medford, Walpole, Westford, and Cambridge Public Schools; Community)
The active study procedures for both Phase 0 and Phase 1 will be identical with the exception of added cognitive assessments and parent/guardian questionnaires for Phase 1 of the study. Phase 1 will not begin until the completion of Phase 0. Interested participants under the age of 18 who provide informed assent and have a parent/guardian who provides informed consent, and participants over the age of 18 who provide informed consent, will be enrolled in the active phase of the study. All participants will complete identical study procedures.

Upon study enrollment participants will be placed into either the high or low payment schedule. All participants will complete 26 study visits, which will be spaced across approximately six months, or 24 weeks (see Study Schema and Time and Events table), and will be conducted confidentially at the participant's school or in the laboratory at MGH. In rare circumstances (eg. shortage of available rooms on school campus), we may request that study visits be conducted in a private space in the near-by public library. Parents of students under the age of 18 who are recruited from one of the participating schools will be notified ahead of time for any visits not conducted on school grounds.

Scheduled Visits (Approximately 10 to 120 minutes per visit). The first week of the study will consist of three visits: an initial baseline visit (during which eligibility will be re-confirmed), a mid-week visit (Visit 2), and a visit occurring approximately 1 week following baseline (Visit 3). Participants will then complete visits occurring at Week 2 (Visit 4) and every week thereafter, totaling 26 scheduled visits. The main objective of Phase 0 will be to assess the acceptability and feasibility of a contingency management protocol for long-term abstinence and to pilot two competing payment schedules. Visits will therefore be brief and impose minimal burden on participants. All scheduled visits during this phase will only consist of self-report questionnaires, semi-structured assessments of mood and substance use, and urine drug tests to verify abstinence. During Phase 1 of the study, cognitive testing will take place at scheduled visits occurring at baseline (Visit 1), Week 4 (Visit 6), Week 8 (Visit 10), Week 12 (Visit 14), Week 16 (Visit 18), Week 20 (Visit 22), and Week 24 (Visit 26). In addition, parents/guardians will be asked to answer brief questionnaires about their child's behavior and mood during Phase 1 at scheduled visits occurring at baseline (Visit 1), Week 4 (Visit 6), Week 12 (Visit 14), and Week 24 (Visit 26).

At the baseline visit (Visit 1), all participants will be using cannabis as usual. At the end of baseline, all participants (N=20) will be asked to abstain from cannabis use for six months and will complete a behavioral contract[26] that lists behaviors to be monitored, schedule of monitoring, and contingencies to be imposed (see section X for more details on payment contingencies). All compensation for attendance will be distributed at the end of each study visit, and will be distributed between study visits for abstinence.

Cannabis abstinence will be indexed by self-reported non-use and, given cannabis' long half-life, by progressively decreasing quantitative levels of 11-nor-delta-9-THC-9-carboxylic acid (THCCOOH), the primary cannabis metabolite, in urine. Residual cannabinoid excretion will be differentiated from new cannabis exposure using a statistical model developed by Schwilke and colleagues.[27] This model was empirically derived from urine CN-THCCOOH concentration ratios of consecutively collected specimen pairs (current specimen/prior specimen). This model takes into account the time between collection of specimens, which enhances the accuracy of prediction of new cannabis use.[28-30] This formula yields an expected CN-THCCOOH ratio associated with specimen pairs during abstinence, and observed ratios that exceed this expected value are interpreted as new cannabis use.

All study procedures will take place at the participant's school or in the laboratory at MGH, with the exception of laboratory processing of cannabis metabolites, which will be conducted at Dominion Diagnostics.

Assessment Techniques
See Time and Events Table for a detailed schedule of assessments administered by visit and by study phase.

Adolescent Questionnaires: Participants will complete self-report measures addressing the following construct areas: demographics; cannabis use behavior and history of cannabis use; cannabis dependence; cannabis motives and expectancies; cannabis withdrawal; current and past use of other substances of abuse (e.g., tobacco, alcohol); peer support; social networks; social integration; exposure to risky peer networks; coping; depressive and anxiety symptoms; delinquent behaviors; temperament; and sleep. The questionnaires are designed to be completed during the protocol visits and are estimated to take anywhere from 10 minutes to 45 minutes to complete depending on the study visit. Participants will be asked to complete all questionnaires at the baseline visit (Visit 1). Additionally, certain measures that may be sensitive to fluctuations over a six-month period will also be completed at subsequent visits. Such questionnaires may include items relevant to cannabis withdrawal, craving, and mood. If the participant prefers, some surveys may be sent electronically via secure REDCap survey links to complete outside of study visits to reduce the length of visits. Participants will have the option to complete all surveys during visits if they choose. Participants will enter data directly into REDCap electronically and will initial and date at the end of each survey to indicate that they inputted this information. In special warranted cirumstances, participants will complete questionnaires using pen and paper and study staff will enter the data into REDCap on their behalf.

Parent/Guardian Questionnaires (Phase 1 only): The parent/guardian questionnaires assess parent/guardian perceptions of the adolescent participant's behavior, emotional functioning, and executive function capabilities. These questionnaires can be completed by the parent/guardian in-person, or sent home electronically (via secure REDCap survey links) or by mail. Parent/guardian questionnaires will be completed at baseline (Visit 1), as well as Week 4 (Visit 6), Week 12 (Visit 14), and Week 24 (Visit 26); they are expected to take no more than 20 minutes to complete. The parent/guardian will enter data directly into REDCap electronically and will initial and date at the end of each survey to indicate that they inputted this information. If necessary (e.g., survey is sent home by mail), the parent/guardian will complete questionnaires using pen and paper and study staff will enter the data into REDCap on their behalf.

Adolescent Interviews: At baseline (Visit 1), participants will complete a 20-minute semi-structured timeline follow-back interview. The purpose of this interview is to retrospectively create a calendar of cannabis episodes as well as other substances of abuse over the previous 90 days. To complete the calendar, MGH staff will work with adolescents to identify both the days when they used substances and the substances used on each day. To gather this information, staff will use a modified version of the timeline follow-back procedure that has been successfully used in other studies with adolescent substance users. This includes identifying important dates or events that stand out to the participant (e.g., start/end of school, family vacations, parties, dances, etc.). At all following visits, participants will complete this timeline follow-back interview but substance use will only be assessed in the time interval since their previous visit. Participants will also complete and the Adolescent

Social Network Assessment to provide a summary of how and with whom they spend their time in their everyday lives. We will ask them to complete this assessment at every visit as this may change throughout their study participation.

Cognitive Testing:
In Phase 0 of the study, we will administer a small cognitive battery to ensure that feasibility of six months of abstinence is not compromised by the addition of cognitive testing to Phase 1. We are proposing to administer the California Verbal Learning Test (CVLT-II), the Wechsler Adult Intelligence Scale (WAIS-IV), and the Rey-Osterrieth Complex Figure Test (ROCFT), which tap into similar domains assessed in the CANTAB battery administered at Phase 1. These tasks are standardized and provide normative data, and will be administered at baseline (Visit 1), Week 4 (Visit 6), Week 12 (Visit 14), and Week 24 (Visit 26).

In Phase 1 of the study, we will explore whether six months of cannabis abstinence may be associated with changes in neurocognitive functioning such as verbal learning/memory, attention, working memory, and complex decision-making. Studies show differences in these domains between cannabis users and non-users.[31-32] Additionally, the neurobiological substrates typically implicated in performance on these tasks (e.g., prefrontal cortex, fronto-subcortical circuitry) undergo the most protracted development during adolescence and may therefore be most susceptible to insults from exogenous cannabinoids. We are proposing to do much of the cognitive testing with the Cambridge Neuropsychological Test Automated Battery (CANTAB). We specifically selected the CANTAB, which is a "state-of-the-art" cognitive battery, based on several criteria to address practical and methodological concerns that may arise from a longitudinal, non-laboratory study. First, the CANTAB has been validated in many populations (including substance using adolescents[33]) and normative data are available. The CANTAB is also administered on a small computerized touch screen tablet, which allows for easy portability, efficient testing of many people (essential for study feasibility), and standardized administration. Third, tests have been adapted from animal model paradigms to increase translatability of findings and tests can be analyzed based on their cognitive components to more readily define impaired and spared cognitive capacities. Next, neuroimaging studies are available that show reliance on neural circuitry implicated in cognitive functioning and addiction. Finally, the CANTAB has been validated longitudinally and offers the unique advantage of parallel forms for retest. The cognitive battery will be administered at the baseline visit (Visit 1), Week 4 (Visit 6), Week 8 (Visit 10), Week 12 (Visit 14), Week 16 (Visit 18), Week 20 (Visit 22), and Week 24 (Visit 26).

Drug Testing: Participants will provide a urine sample at all study visits to qualitatively screen for cannabis use as well as other substances of abuse and to quantitatively screen for amount of THC metabolites in urine.

Due to the negative impact that recent outside drug or alcohol use could have on a subject's performance in the cognitive testing and responses to questionnaires/interviews, subjects will be asked to refrain from the use of any illicit drugs or the consumption of alcohol on the day of the study visits, with the exception of nicotine/tobacco or caffeine. This short-term abstinence will be assessed using participant self-report at each visit.

Phase 0 Time and Events Table

	V0	**V1**	**V6, 14, 26**	**V2-5, 7-13, 15-25**
	PS	**BL**	**Wks 4, 12, 24**	**Wks 1-3, 5-11, 13-23**
Screener	X			
Background Questionnaire		X		
Psychopathology Questionnaires				
Safety Monitoring—CHRT		X	X	X
Marijuana Questionnaires				
Dependence—CUDIT-R		X		
Problems—MPS		X		
Craving—MCQ-SF		X	X	X
Withdrawal—CWS		X	X	X
Motives—MMM		X		

Other Questionnaires				
Exercise – GLTEQ		X	X	X (except V2)
School Engagement—mSESQ		X	X	X (except V2)
Academic History—SHQ		X		
Sleep—PSQI		X	X	X (except V2)
Activity Involvement—mYLSBQ		X	X	X (except V2)
Interviews				
Peer Network—ASNA		X	X	X
Timeline Follow-Back—TLFB		X	X	X
Cognitive Tests				
CVLT-II		X	X	
WAIS-IV		X	X	
ROCFT		X	X	
Lab Tests				
Urinalysis		X	X	X
Genetics—Saliva Sample		X		
Estimated Time for Completion (mins)	**10**	**120**	**60**	**10**

Note: BL, Baseline; PS, Phone Screening; Wks, Weeks

Phase 1 Time and Events Table

	V0	**V1**	**V2, 3, 4, 8, 10, 12, 14, 16**	**V6, 14, 26**	**V10, 18, 22**
	PS	**BL**	**Mid-Wk, Wks 1, 2, 6, 10, 14, 18, 22**	**Wks 4, 12, 24**	**Wks 8, 16, 20**
Screener	X				
Background Questionnaire		X			
Psychopathology Questionnaires					
Childhood Sx Checklist—Childhood ADHD		X			
Current Sx Checklist—Current ADHD		X		X	
Current Mood—MASQ		X		X	X
Depression—CES-DC		X		X	X
Safety Monitoring—CHRT		X	X	X	X
Self-Report of Personality—BASC-3 SRP		X		X	
Parent Report of Personality—BASC-3 PRS*		X		X	
Cognition Questionnaires					
Executive Functioning—BRIEF Self-Report		X		X	
Executive Functioning—BRIEF Parent-Report*		X		X	
Delay Discounting—MCQ		X		X	X
Peer Conformity—MISS		X		X	
General SU Questionnaires					
Peer Substance Use/Tolerance—PSU		X			
Alcohol Questionnaires					

Dependence—AUDIT		X			
Motives—DMQ		X			
Marijuana Questionnaires					
Dependence—CUDIT-R		X			
Problems—MPS		X			
Craving—MCQ-SF		X	X	X	X
Withdrawal—CWS		X	X	X	X
Motives—MMM		X			
Tobacco Questionnaires					
Nicotine Dependence—PSECDI		X			
Other Questionnaires					
Exercise – GLTEQ		X	X (except V2)	X	X
School Engagement—mSESQ		X	X (except V2)	X	X
Academic History—SHQ		X			
Sleep—PSQI		X	X (except V2)	X	X
Activity Involvement—mYLSBQ		X	X (except V2)	X	X
Interviews					
MINI 7.0 Adult, MINI 7.0 Kid		X			
Timeline Follow-Back—TLFB		X	X	X	X
Cognitive Tests					
CANTAB		X		X	X
Lab Tests					
Urinalysis		X	X	X	X
Genetics—Saliva Sample		X			
Estimated Time for Completion (mins)	**10**	**120**	**10**	**60**	**60**

Note: BL, Baseline; PS, Phone Screening; Wks, Weeks; * indicates questionnaires completed by parents/guardians.

DNA Collection and Analysis

DNA Collection (Saliva): DNA samples will be collected using Oragene (OGR-500) saliva kits. The samples will be sent to Dr. Jonathan Rosand's laboratory at Center for Genomic Medicine (CGM) at Massachusetts General Hospital for DNA extraction and long-term storage (Director: Sekar Kathiersan, MD). Dr. Rosand's laboratory in CGM utilizes a password protected web-based application (www.PNGUtrack.com) to interface with the clinical enrollment sites for sample submission. At the clinical site, samples are labeled with 2D barcode labels which are scanned into a sample submission module of the PNGUtrack system along with basic non-identifying information about the sample (e.g. sex, collection date, sample volume, shipping date, etc.). Samples are shipped to the laboratory where they are logged into an Oracle database (JANE) that serves as the central LIMS tracking database. The JANE database interacts with the PNGUtrack sample submission system and tracks each sample from receipt to extraction to storage.

Participants may be asked to provide a second sample if a re-collect is recommended after DNA extraction (i.e. there is very little DNA in the sample). Participants are not required to provide another sample if they do not wish to do so. If a participant completed our one-month abstinence study (Protocol # 2015P000076) prior to enrollment in this six-month abstinence study and a DNA sample was already collected, a new sample will not be collected and the sample from Protocol #2015P000076 will be used for analysis.

GWAS Genotyping: The Broad Institute will perform molecular profiling (array-based) of subject samples and subsequent in-depth analysis of the data, which will allow us to detect alterations in the genome including point mutations, small insertions and deletions, chromosomal copy number alterations, and translocations. These experiments are intended to help identify candidate genes involved in the physiopathology of neurological and psychological diseases. The molecular information generated from these samples will not be returned to subjects at any time.

Data from this study may result in communications in journals or at scientific meetings. Subjects will not be identified in those communications. To facilitate research, the genetic information generated may upon publication be deposited in protected databases (such as dbGAP) available only to bona fide researchers with specific scientific questions who promise to not try to identify individuals. The data will be sent to these banks in a coded manner and again will not contain any traditionally used identifier such as name, address, phone number, or social security number. Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

The Broad Institute will not be involved in subject ascertainment. Prior to transfer of bio-specimen aliquots to the Broad Institute, samples will be re-encoded at the collaborators institutions. No identifying patient information will be shared with Broad scientists at any time. Some limited clinical data will be obtained from collaborators. Again, all subject identifying information will remain with the collaborators and only de-identified clinical data will be shared with the Broad Institute.

Genetic Data Protection: In addition, steps will be taken to protect confidentiality of genetic data as outlined:

1) All MGH study staff are trained to make confidentiality the first priority.
2) No genetic research data will be entered into the medical record.
3) The results of the genetic analyses will not be shared with participants, their family members or unauthorized third parties.
4) Genetic data are encoded using coded identifiers. These codes, rather than personal identifiers, are used in any analytic datasets. The code key linking coded identifiers to personal identifiers are kept in an access-restricted, password protected electronic file and are not shared with the genetics laboratories.
5) Consent forms are stored in locked cabinets apart from demographic and diagnostic data.
6) Samples and genetic data stored in the laboratory will be identified only by the code numbers and laboratory personnel will not have access to personal identifiers.
7) The most serious risk would be identification of individuals in the publicly shared database. To prevent this, computerized data files provided to other investigators will not include any of the HIPPA-defined personal identifiers. Published material will not identify subjects.

VI. BIOSTATISTICAL ANALYSES

This is a first-of-its kind study using a 6-month contingency management paradigm for cannabis abstinence. As such, pilot testing needs to occur to evaluate feasibility of this paradigm before a larger trial can be proposed. Phase 0 will examine the initial acceptability and feasibility of a contingency management protocol for long-term abstinence, and collect preliminary data on the efficacy of two competing payment schedules. We will calculate continuous abstinence rates at six months. If continuous abstinence rates at six months are low (e.g. below 80 percent) and therefore a larger six-month trial is not likely feasible, we will then examine continuous abstinence rates at each prior month of the study. This will help us determine the longest trial feasible in this population. Phase 1 will collect pilot data on change in cognition with six months of abstinence, using the payment schedule informed by Phase 0. These data will be used to estimate effect sizes and inform a subsequent power analysis for a fully-powered, randomized trial to be proposed at the completion of this pilot study.

VII. RISKS AND DISCOMFORTS

There are a few potential risks to individuals participating in the study.

Psychosocial, Social and Legal risks: There are no uncommon psychological, social, or legal risks associated with participation in this study. There is a slight risk that the questionnaires and interviews may contribute to temporary discomfort when participants are asked about sensitive behaviors or personal feelings (e.g., cannabis use, smoking or mood), but in our experience with similar studies this risk is very minimal. To minimize these risks, all data will be coded with unique subject identifiers to help minimize concerns of confidentiality which may decrease discomfort to respond to questions and interviews truthfully. Additionally, participants will be reminded by MGH study staff that they may omit any questions they do not wish to answer or discontinue their participation at any time. Participants will be told by MGH study staff on the assent/consent form that if they feel distressed after participating and wish to discuss their concerns further, they may withdraw from the study immediately. Research staff will have information on counseling options for trusted treaters in the community available to distribute to participants who request such information. Given that we will be meeting with participants regularly and will be administering validated mood and substance use questionnaires during each visit, we are also uniquely positioned to monitor changes in endorsement of mental health symptoms. For example, we will administer the Concise Health Risk Tracking (CHRT) scale at every visit and a consult with a doctoral level clinical will occur for any participant who endorses passive suicidal ideation (at a level of "Agree" of above) or active suicidal thoughts (at a level of "Neutral" or above). For any participant for whom we have concerns about emotional wellbeing, we will ask him/her if we can discuss this with his/her parents/guardians to help coordinate a plan for monitoring and treatment. Finally, on the unlikely event that a participant is emotionally distressed, MGH study staff is prepared to deal with such a situation should it occur. Our team is comprised of several investigators with significant expertise in mental health issues and is well prepared to handle emergency situations: our investigators are well-trained in psychotherapeutic interventions to help process and mitigate distress and have significant experience assessing for and addressing patient safety. Field staff who collect data will be trained by a licensed psychiatrist (A. Eden Evins, MD, MPH) and licensed clinical psychologist (Randi Schuster, PhD) on identifying and responding to emotional distress in a research participant. The study will be terminated if the clinician or the research team determine that their continued participation is unsafe or not in their best interest, e.g., in circumstances where there is deterioration in their mental or physical health judged to require a change in medication or hospitalization.

Confidentiality and Privacy: Another potential risk to participants is breach of confidentiality but protecting the confidentiality and integrity of our research participants is a top priority for this MGH project. MGH's careful consent and data confidentiality procedures should greatly minimize any potential risk to participants' privacy. Only MGH project investigators and authorized study staff will have access to raw data. Once collected, an individual's data will not be released to anyone outside of MGH authorized project staff. Confidentiality is further assured by assigning a unique identifier to each participant. There will be a restricted access master list of names and other identifying information linked to the identification number. The master list will be kept on a password-protected Partners computer file, separate from other data, along with other materials that have participant's name (e.g., consent forms). No identifying information is listed on participant or parent/guardian questionnaires or any other materials with data on them (e.g., cognitive tests, drug tests), with the exception of participant initials at the end of questionnaires to indicate that participants completed them directly. Participants will complete self-report questionnaires directly on REDCap using a Partners-encrypted device, which greatly minimizes the likelihood of confidentiality breaches. Only authorized MGH project members will be allowed access to this computer. Any raw data files in electronic format will be housed on our network server at the Center for Addiction Medicine at MGH and will be password protected so that only authorized project personnel have access to them. These files will not have participant names or identifying information attached to them and no information will appear in hospital medical records. Given that this pilot study is only recruiting adolescent cannabis users, it is possible that parents/guardians will become aware of their child's cannabis use history by signing the consent form. However, potential participants will be made aware of this during the telephone screening and have the option to decline parent/guardian contact, and therefore decline enrolling in the study. Additionally, both participants and parents/guardians will be made aware that no details disclosed during the study, including those relevant to use history, will be shared with the parents/guardians unless there is an immediate concern for safety.

In the consent/assent forms, both parents/guardians and participants are informed that only in emergency situations (in which an individual is at immediate risk for harm) would we release any information. Specifically, if a participant tells us that he/she has intent and/or a plan to cause harm to self or other, we will tell the parents/guardians and call 911. If a participant discusses details about ongoing child abuse, we will report such abuse to the Department of Child and Families directly. If we learn about mood concerns or problematic substance use, we will provide the participant with local and trusted resources for follow-up consultation and we will ask him/her if this information can be disclosed to his/her parents/guardians to help coordinate and facilitate care. Finally, when the results are published or discussed in conferences, no information will be included that would reveal an individual participant's identity. All data will be analyzed on a group-level and not by individual participants.

We believe that staff training is one of the most important ways we can protect our participants from potential risks. Staff will participate in intensive training which will be led by Drs. Evins (licensed psychiatrist) and Schuster (licensed clinical psychologist) before data collection begins with readings, lectures, role-playing, and group discussions. Staff members who collect data will meet with senior investigators on a weekly basis during assessment points to discuss any issues, review procedures, and conduct ongoing training on these important issues.

A Certificate of Confidentiality from the National Institutes of Health has been obtained for this study. We can use this Certificate to legally refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. We will use the Certificate to resist any demands for information that would identify participants, except in the instances of child abuse and neglect, or harm to self or others.

A. **Special Considerations for Participants Recruited from Schools**: Parents and staff members at participating schools will not be provided any information regarding study participants, including cannabis use habits, unless there is deemed risk to self or others. In the consent/assent forms, both parents and students are informed that only in emergency situations (in which an individual is at immediate risk for harm) would we release any information. Specifically, if a participant tells us that he/she has intent and/or a plan to cause harm to self or other, we will tell the parents and call 911. If the participant says that he/she has recurrent thoughts about harming him/herself or someone else but does not have intent or a plan to do so, we will notify the parents and other appropriate medical or counseling personnel. Finally, if a participant discusses details about ongoing child abuse, we will report such abuse to the Department of Child and Families directly. If we learn about mood concerns or problematic substance use, we will provide the participant with local and trusted resources for follow-up consultation and we will ask him/her if this information can be disclosed to his/her parents to help coordinate and facilitate care. Additionally, schools that serve as research sites will not be identified and only minimal information about their characteristics will be released. Finally, when the results are published or discussed in conferences, no information will be included that would reveal an individual student's identity or the name of the school at which the research was conducted. All data will be analyzed on a group-level and not by individual participants.

VIII. POTENTIAL BENEFITS

We believe that this research study will help engage participants in meaningful and important research with immediate potential benefits to both the individual student and the larger community, will provide for unique opportunities for education and outreach, and will yield valuable information that will allow schools to develop and integrate prevention programs that are custom-fit to their community needs.

Participants may find that talking about cannabis use increases their awareness of any issues related to drug use. Additionally, this project may help several adolescents stop using cannabis even though they may not be seeking treatment. At the end of the six-month abstinence trial, we can connect participants to treatment resources if desired by the participant, which will help promote longer-term abstinence. Finally, our experience with adolescents participating in similar research is that they often enjoy the opportunity to interact with field

staff, to engage in an interesting self-study, and to feel as if they are contributing to research on the lives of teenagers.

Information developed from this study may help researchers in the future, and will directly inform the development of a fully-powered trial. There is much to be learned from the project including: determining understanding of the feasibility and efficacy of a long-term abstinence protocol, as well as of the impact of cannabis on cognitive functioning among adolescents, which represents a large and critical gap in the extant literature. This pilot study, therefore, is critically needed to determine whether a larger and more comprehensive study with a six-month contingency management intervention could be feasibly conducted. This larger project, informed by the current pilot study, will directly test whether six months of cannabis abstinence is associated with meaningful improvements in cognition, mood, and academic functioning.

The greatest benefit will be to future cohorts of adolescents who will benefit from what is learned from this research project. Knowledge from this pilot study and the subsequent fully-powered trial will likely directly inform development of prevention and cessation programs that are engaging and effective for adolescents.

IX. MONITORING QUALITY AND ASSURANCE

All participants will have direct contact information for the principal investigator if they have questions at any time. Dr. Schuster is responsible for the overall management of the study and will maintain regular communication with all the study staff. The principal investigator will meet weekly with all study investigators to review the details of data acquisition and analysis as well as any minor problems. In the event of any minor or significant adverse event, the principal investigator will be contacted immediately. The principal investigator is responsible for the generation of summary reports documenting this process and outcomes which will be included in the Continuing Review reports to the IRB.

Serious adverse events are not expected because of study procedures. Should one occur, it will be reported by telephone or email by the principal investigator to the Partners IRB per current PHRC Adverse Event Reporting Policy. All adverse events (if not serious) will be reported in writing to the Partners Human Research Committee. All information regarding experimental subjects will be kept in the offices of the principal or co-investigators. All data will be identified by a unique code number.

X. PARTICIPANT COMPENSATION

All participants will be paid by reloadable cards for their participation and abstinence. Reloadable cards will be managed by CT (Clinical Trials) Payer. CT Payer is a secure web-based platform that facilitates "HIPAA & HITECH safe" clinical trial and study-related payments onto prepaid reloadable MasterCards. Unlike payment systems offered by banks and third-party payment providers, CT Payer does not collect any protected health information from research participants. CT Payer has been approved as a payment method by research management and has been used successfully for the past 3 years by a similar protocol in our laboratory (PI Dr. Schuster, Protocol #: 2015P000076).

Phase 0: Participants will be reimbursed using one of two different payment schedules, both escalating based on continuous cannabis abstinence (indexed by self-reported non-use and progressively decreasing quantitative levels of urine THCCOOH). Compensation for attendance to the baseline visit (Visit 1) will be distributed at the end of the study visit, and all compensation for abstinence will be distributed between study visits upon receipt of laboratory results from Dominion Diagnostics. Participants are reset to the starting level if abstinence is not demonstrated within the first week of study participation. If a participant fails to demonstrate abstinence at any point between Week 1 (Visit 3) through the last visit, they will be discontinued from the study based on non-compliance with study protocol.

The schedule of reimbursement for session attendance and abstinence (see payment schedule below) was informed by the payment schedule utilized by our current one-month abstinence protocol (Protocol #: 2015P000076). In our one-month abstinence protocol, the schedule of reimbursement is what has been found effective in similar populations.[34-38] All participants will be paid 10 dollars for attending the Baseline visit (Visit 1). After the initial baseline visit, the "Low" payment group will receive payments escalating 2 dollars for each subsequent visit with verified abstinence (e.g., $12, $14, $16). The "High" payment group will receive

escalating payments of 3 dollars for continuous abstinence following the baseline payment (e.g., $13, $16, $19). The schedules of reimbursement for session attendance and abstinence for the current six-month study -- $910 or $1,235 – are *more* conservative than the amount of reimbursement estimated should payment from our one-month abstinence protocol be extended to six months. That is, the current protocol proposes to compensate more than $4,300-4,600 less than that estimated should the compensation schedule from Protocol #2015P000076 be extended to six months.

The total amount of reimbursement is thought to be appropriate in this population for the following reasons: 1) parents/guardians will be aware of the amount of money that participants can potentially earn by participating in the study; 2) all participants will be incentivized to abstain from a health-compromising behavior, that is continued use of cannabis; 3) CT Payer greatly minimizes risk of funds being used for illegal purchases.

The table below details the maximum potential earnings; however, the total amount earned will depend on the number of sessions attended, and also for evidenced cannabis abstinence.

Phase 0 Schedule of Compensation

Month	Visit Number		Schedule	
			Low	High
1	0	Screening	$0	$0
	1	Week 0 (V1)	$10 (attendance)	$10 (attendance)
	2	Week 0 (V2)	$12	$13
	3	Week 1 (V3)	$14	$16
	4	Week 2	$16	$19
	5	Week 3	$18	$22
	6	Week 4	$20	$25
2	7	Week 5	$22	$28
	8	Week 6	$24	$31
	9	Week 7	$26	$34
	10	Week 8	$28	$37
3	11	Week 9	$30	$40
	12	Week 10	$32	$43
	13	Week 11	$34	$46
	14	Week 12	$36	$49
4	15	Week 13	$38	$52
	16	Week 14	$40	$55
	17	Week 15	$42	$58
	18	Week 16	$44	$61
5	19	Week 17	$46	$64
	20	Week 18	$48	$67
	21	Week 19	$50	$70
	22	Week 20	$52	$73
6	23	Week 21	$54	$76
	24	Week 22	$56	$79
	25	Week 23	$58	$82
	26	Week 24	$60	$85
		Totals	$910	$1235

Participants may also receive reimbursement for transportation to our center in Boston. They may receive $2.00 per ride on the bus or $2.90 per ride on the subway. Payment will be provided on the CT Payer reloadable card on the day of the study visit. If a parent accompanies their child to the study visit, they may be

reimbursed for transportation at the same rate. Parking vouchers are also available for participants or their parents who drive to our center and park in an MGH parking garage.

The payment schedule for Phase 1 will be informed by data collected during the Phase 0 pilot period. This protocol will be amended upon completion of Phase 0 to designate the payment schedule to be employed.

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