A Digital Intervention to Prevent Initiation of Opioid Misuse in Adolescents in School-based Health Centers

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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
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Protocol Title: A digital intervention to prevent the initiation of opioid misuse in adolescents in school-based health centers

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Version Date: March 8, 2021

(*If applicable*) Clinicaltrials.gov Registration #: Click or tap here to enter text.

INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.
2. If a section or question does not apply to your research study, type "Not Applicable" underneath.
3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   Most opioid misuse begins during adolescence and young adulthood. Adolescence is the time to intervene with prevention interventions (i.e., interventions focused on adolescents who have not yet misused opioids) in settings like school-based health centers (HCs), yet few interventions exist that prevent initiation of opioid misuse. "Serious videogame" interventions can improve health behaviors. They meet adolescents "where they are," and compared to standard interventions, they can reach large populations, with consistent fidelity, place limited demands on personnel/resources, and facilitate rapid sustainable distribution, all at a potentially lower cost. This study harnesses the power of videogame interventions and incorporates components of effective substance use prevention programs to develop an evidence-informed intervention to prevent the initiation of opioid misuse in adolescents. Building on our experience developing videogame interventions and in partnership with the national School-Based Health Alliance (SBHA), we will develop and test a new videogame intervention, *PlaySmart*. *PlaySmart* will build upon our *PlayForward* videogame intervention platform that has demonstrated efficacy in improving attitudes and knowledge related to risk behaviors. Through rigorous formative work and with input from adolescents, and our SBHA and game development partners, we will create the *PlaySmart* videogame intervention. *PlaySmart* will be designed to provide players with behavioral skills and knowledge through repetitive and engaging videogame play to target adolescent perception of risk of harm from initiating opioid misuse. The specific aims of this proposal are to: 1) develop the *PlaySmart* game and implementation strategies through focus groups as part of our formative work; and 2) pilot-test the *PlaySmart* game. We will be working with local schools as well as SBHA stakeholders and partners. The gap in the research on preventing initiation of opioid misuse in youth and in implementing prevention programs with good fidelity needs to be urgently addressed given the high prevalence of adolescent opioid misuse and overdose. This research has the potential to create a videogame intervention to prevent initiation of opioid misuse with far-reaching and sustained impact on adolescents.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   The probable duration of the project is 2 years. This timeline includes formative work (e.g., focus groups and interviews), the development of a new videogame in conjunction with our videogame development partners, and piloting/playtesting of the new videogame upon completion of development.

	Year 1		**Year 2**	
Develop ***PlaySmart*** videogame intervention				
Conduct/transcribe focus groups and interviews	X			
Analyze data and refine logic model	X	X		
Develop manuals (Game Playbooks) and digital game intervention	X	X	X	
Pilot-test game intervention, develop user's manual, pilot processes for subsequent RCT (during next phase of research)		X	X	**X**

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Drug overdose is now the leading cause of death in those under the age of 50. According to the Centers for Disease Control and Prevention (CDC), 130 Americans die every day from an opioid overdose[1]. These overdose mortality rates reflect the increase of opioid misuse in this country and of particular concern, is that they translate to adolescents. Opioid overdose deaths among adolescents aged 15–19 increased 253% between 1999 and 2016[2]. Importantly, close to 40% of prescription opioid misuse and 68% of heroin use starts in adolescence and young adulthood[3]. Given the importance of this problem to the health and future of our youth, it is imperative to develop and implement effective strategies to prevent the initiation of opioid misuse in youth. The current situation demands high quality, evidence-informed programs that can be rapidly deployed with good fidelity. To date, programs created to prevent substance use initiation overall (e.g., alcohol, marijuana, and tobacco) do not have much impact in terms of effectively preventing initiation of opioid misuse. Further, there is conflicting evidence on the effectiveness of substance use prevention interventions, particularly those conducted in schools where many of these programs are deployed[4]. Novel ways to reach this highly vulnerable population in settings such as the over 2600 school-based health centers (school-based HCs) are needed.

Videogames as interventions have the advantage of meeting adolescents "where they are." Over 90% of adolescent boys and girls play videogames[5]. "Serious games," defined as games for a primary purpose other than entertainment, have been developed by our group and others and there is compelling evidence that they promote health and are effective at prevention[6-9]. Serious videogames are an ideal prevention platform, facilitating opportunities for repetitive interactions to acquire and rehearse new skills that can transfer to real-life situations[10,11]. They can reach large populations, with consistent fidelity, place limited demands on personnel/resources, and facilitate rapid sustainable distribution, all at a potentially lower cost. To date, no effective serious videogame interventions to prevent initiation of opioid misuse have been developed. While gaming addiction is a recognized entity, it is very rare and, in the setting of playing a serious game, very unlikely. If there are any concerns of developing serious addictive behaviors in our pilot study participants, we have team members who are experts in the field of addiction medicine and will address these issues immediately. We will build on our experience developing and evaluating serious videogame interventions (R01 HD062080; R41 HD088317, 2R42 HD088317, 5P50 DA036151)[6-9,12-26] to develop a videogame intervention designed to prevent initiation of opioid misuse in adolescents. We will conduct formative work with our target audience and content experts to create a new videogame intervention, *PlaySmart*, focusing on preventing initiation of opioid misuse in older adolescents, aged 16-19. Content experts include those from building out the foundation of *PlayForward: Elm City Stories* that targets youth HIV prevention[7] and *PlayForward: smokeSCREEN* that targets youth smoking prevention[8]. We will build the conceptual model[19] to promote healthy decision-making using constructs from the theory of planned behavior[27], social learning and self- efficacy theories[28,29], and principles from message framing[30] grounded in prospect theory[31] that have been shown to impact prevention. We will focus on antecedents of opioid misuse including perceived harm, intentions, self-efficacy, and initiation of opioid misuse. This study is consistent with objectives outlined in the proposed National Institute on Drug Abuse 2016-2020 Strategic Plan in that it will "develop and test innovative prevention interventions that target mechanisms underlying risk factors" exploring the "potential of technology-based methods for delivering prevention interventions, such as smartphones, video games, and social media." It also focuses on the "vulnerability for substance use and related problems…shown to peak during critical life transitions[32]" as seen in high-risk adolescents.

Our study's specific aims are to:

1a: Develop the *PlaySmart* game through focus groups with up to 40 16-19-year old high school students, focus groups with up to 20 18-25-year-old young adults, interviews with up to 20 16-25-year olds, interviews with up to 20 opioid use disorder treatment providers and focus groups with up to 20 stakeholders (educators, prevention specialists, etc.).

1b: Pilot-test *PlaySmart* with 30 adolescents, using methods from our prior research [13,16,19,20,33]

1c: Develop implementation strategies and partners through focus groups with 50 School Based Health Alliance affiliates and 30 adolescents from the Youth Advisory Council.

4. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

This protocol will be conducted over two years. The outline below highlights the research plan. We will conduct focus groups and interviews to help inform the development of a digital intervention and then evaluate the feasibility, acceptability, and usability in a pilot study. Eight focus groups with five adolescents (n=40), aged 16-19, will be conducted locally over the course of six months. Each group will meet once for approximately 1-1.5 hours after school in a classroom. When the study is introduced to parents/guardians and students, we have always stressed that a stipulation of our studies requires reliable transportation to/from our studies. In certain cases where transportation is not available, we will provide a bus pass.

In addition, we will conduct 4 focus groups with approximately five18-25-year-old young adults (n=20). Each focus group will meet once for approximately 1-1.5 hours at a private location on a college campus, a public meeting space such as a library, or in a location at Yale Medical School. All participants will provide consent. Our goal is to learn about the perceptions and experiences of opioid misuse among young adults to inform our intervention.

Additionally, we will conduct annual focus groups for approximately 1-1.5 hours in a private room at the annual School-Based Health Alliance Convention with 15 participants in the Youth Advisory Council (e.g., high school and college aged) and 25 participants who are school-based health affiliates (i.e., national representatives of school-based health centers who are adults) in June 2020 and June 2021. Since the Youth Advisory Council is part of an existing council within the national organization, we will share the details of the study with this group by working with the SBHA before the start of the Convention. A representative from the SBHA will email (see email in documents section) members of the Youth Advisory Council up to three times. In the first email, the representative will share details about the study and how to contact our team if one chooses to participate voluntarily. If the study team is contacted, youth will provide verbal assent/consent over the phone. If youth are minors, it will be explicitly stated that parental/guardian verbal consent over the phone is required prior to participation. If email was sent three times and the person did not respond, our team will respect their wishes of not wanting to participate. The Youth Advisory Council is an established group that is part of the SBHA and, therefore, contact with parents/guardians is common for those who are minors.

In addition, we will aim to conduct up to 20 individual interviews with adolescents and young adults (aged 16-25) who are currently receiving treatment for opioid use disorder. Interviews will last approximately 60-90 minutes for one session and will be conducted virtually. Some may be asked to provide written stories during interviews if time allows. All writing will be de-identified. Interviews will be conducted by the team's research staff. Informed assent will be obtained from participants between the ages of 16-17 in addition to their informed consent from their parent/guardian. Informed consent will be

obtained from individuals aged 18 and over. Interviews will be audiotaped, and participants will be instructed to not share any identifiable information in the interview. Our goal is to learn from adolescents and young adults who are currently in treatment for opioid misuse/opioid use disorder, their perspectives and stories as well as key aspects, skills, and any other ideas from their views of the past to build out an effective and relatable intervention. For clarification, the purpose of this interview is to learn about their past stories and suggestions related to prevention. These interviews are by no means to learn about experiences in treatment.

We will also conduct up to 20 interviews with treatment providers of opioid use disorder that have provided medical services to individuals aged 16-35 in the last 5 years. Interviews will last approximately 60-90 minutes for one session and will be conducted virtually. Interviews will be conducted by the team's research staff. Information sheets will be given to the treatment provider and verbal consent will be obtained. Interviews will be audiotaped, and participants will be instructed to not share any identifiable information in the interview. We will record the audio of the virtual interview. The participants name will not be recorded during the virtual interview and the tapes will be coded by a number rather than a name to protect their confidentiality. Our goal is to learn from treatment providers, their perspective about what should be included in a game that aims to prevent opioid misuse in adolescents. In addition, we aim to learn de-identified, generalized stories of patients they treat, in order to inform the storylines and characters of our videogame prevention intervention.

Lastly, we will conduct focus groups with up to 20 stakeholders (educators, prevention specialists, etc.) aged of 19-80. Focus groups will be approximately 60-90 minutes in length for one session and will be conducted virtually by the team's research staff. Information sheets will be given to the stakeholders and verbal consent will be obtained. Focus groups will be audio taped and participants will be instructed to not share any identifiable information in the focus group. The audio of the virtual focus group will be recorded. Participants names will not be recorded during the virtual focus group and tapes will be coded by a number to protect confidentiality. Our goal is to learn from stakeholders, perspective on what should be included in a game that aims to prevent opioid misuse in adolescents. In addition, we aim to learn development and implementation strategies from these stakeholders.

All focus groups and all interviews will be conducted locally. They, along with those at the annual School-Based Health Alliance Convention, will inform the development of this videogame intervention and will be audiotaped. All participants will receive instructions on not using identifiable information (e.g., names, school, peer/colleague names, etc.) while being audiotaped and will be provided a study number prior to the start of audiotaping and will be instructed to state their study number prior to speaking.
Audiotapings will be transcribed and will be destroyed 24 months after the completion of the study and after review of their content has been completed. Transcriptions will not be sent to other institutions and will not be used for purposes other than this study.

The entire pilot study phase for this project will be completed over the course of six months. We plan to enroll 30 adolescents, aged 16-19 to playtest our game. We will meet with participants between 2-4 times for approximately 1-1.5 hours each time, over the course of two to four weeks. Participants will complete baseline measures, two gameplay sessions and a post-assessment to measure feasibility, acceptability, and usability. Each participant will complete the pilot study within two to four weeks. We will meet with them after school in a classroom (securing room with coordination from our school partners). When the study is introduced to parents/guardians and students, we have always stressed that a stipulation of our studies requires reliable transportation to/from our studies. In certain cases, we will provide a bus pass.

All participants will be assigned a study identification number to link pre/post assessments and to conduct focus groups. Data collection and storage will be conducted according to standardized protocols. The link between participant's identity and the study number is confidential and will be kept separate from all study data. Research data, such as informed consents/assents, transcriptions, and field notes, is kept in cabinets that are locked except when in use, and access to

data stored in computers is password protected. We will collect participants' names, school, gender, grade level, age, race, and ethnicity. Names will not be sent to any third parties. Any data shared with NIH or other third-party organizations will be aggregate data. We will collect this information and it will be stored in a secured database.

The Yale University Human Subjects Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records**.** All published results will be group data. Information that will be collected during the focus group interviews will be erased 12 months after the completion of the study and after review of their content has been completed.

1. **Formative and development work**: (1 year)
    a.) We will work iteratively with our target audience of 16-19-year old adolescents within schools to develop videogame content, collecting qualitative data for the videogame intervention and refining our logic model with input from 8 focus groups of 5 adolescents each (n=40), aged 16-19 and 4 focus groups of 5 young adults aged 18-25 (n=20).
    b.) We will aim to conduct up to 20 individual interviews with participants who are aged 16-25 and who are currently receiving treatment for opioid use disorder to learn about their stories and experiences to develop videogame content, collect qualitative data for the videogame intervention, and refine our logic model with input from participants.
    c.) We will aim to conduct up to 20 individual interviews with treatment providers of opioid use disorder that have provided medical services for individuals aged 16-35 within the last 5 years to learn about their stories, experiences and perspectives to develop videogame content, collect qualitative data for the videogame intervention, and refine our logic model with input from participants.
    d.) We will aim to conduct focus groups of 5-6 individuals of up to 20 stakeholders (educators, prevention specialists etc.) aged 19-80 to learn about their experiences and recommendations to develop videogame content and refine our logic model.
    e.) We will create the "Game Playbook" specific to this new ***PlaySmart*** intervention. Game Playbooks are our **intervention manuals**. We create behavior change gameplay manuals to accommodate the specific needs of a multi-disciplinary game development team. The playbooks outline the theoretical foundations and gameplay elements. This ensures targeted theoretical principles and behavior change mechanisms are included in the videogame intervention.

    f.) We will **adapt and refine** the current ***PlayForward*** **Platform** to develop the new ***PlaySmart*** game intervention by creating new content, developed from focus groups and from the substance use prevention literature, for our game development team, Schell Games, to adapt the current platform to develop the new ***PlaySmart*** game.

    g.) While developing the game content, we will simultaneously be finalizing our **assessment measures**. This strategy ensures that what we are testing is in the content of the game and that the game provides the information and skill-building that our measures will assess. Once we have finalized our assessment measures, we will have them loaded into REDCap, the Web-based computer system that will be managed by our collaborators at the Yale Center for Analytical Sciences (YCAS), and this system will be used for data collection, management, and monitoring.

2. **Pilot feasibility and acceptability work:** (1 year)
    a.) We will work iteratively to develop videogame content, conducting 8 **focus groups** of 5 adolescents each (n=40), aged 16-19 and 4 focus groups of 5 young adults each (n=20), aged 18-25 collecting qualitative data for the videogame intervention and to refine our logic model.
    b.) Working with our community school partners, we will engage 1-2 schools and school-

based health centers to **recruit** 30 adolescents for our subsequent pilot study. Given participants are only involved in the pilot study for several weeks and given our track record of having retained the majority of participants for over two years of a prior RCT, we are not concerned about retention.

c.) We will **pilot-test** the intervention with 30 adolescents, aged 16-19, in conjunction with their schools, to evaluate the **acceptability** of the game. To garner feedback, we will collect data (both qualitative and quantitative) after the completion of game play sessions. The pilot will either be conducted virtually or in person. For the in person segment of the pilot, all COVID-19 protocols and procedures that are in place at our partner school site will be followed.

d.) We will also **pilot procedures** such as assuring the gameplay sessions go smoothly and that data collection is streamlined in anticipation of conducting the subsequent RCT.

e.) We will develop a game implementation manual that will be used during the subsequent RCT, as needed, by school and school-based health center staff.

f.) As part of our focus groups with school-based health affiliates, we will collect focus group data for our formative and development of a videogame intervention from the Youth Advisory Council (n=15) and School-based health affiliates (n=25) at the annual School-Based Health Alliance Convention. This includes data on implementation strategies such as barriers and facilitators and to share perceptions of the newly created game and provide input on the game implementation manual. This will take place at the annual School-Based Health Alliance Convention with our national partners who will help recruit participants for the Youth Advisory Council and School-Based Health Alliance.

They will assist in recruitment to create two focus groups: 1) youth and college- aged adults in the Youth Advisory Council (i.e., an already established group), 2) members who are affiliated with school-based health centers. We will conduct focus groups for approximately 1-1.5 hours once per year for two years in a private room at the Convention with up to 15 participants in the Youth Advisory Council (e.g., high school- and college-aged-participants) and 25 participants who are school-based health affiliates (i.e., national representatives of school-based health centers who are adults) in June 2020 and June 2021. Recruitment will consist of sending out flyers via email and making announcements via email to all involved in the Youth Advisory Council as well as making an announcement to those who are affiliated with the School-Based Health Alliance via the School-Based Health Alliance listserv before the Convention. For this reason, they will be prepared to participate before they arrive at the Convention.

5. Genetic Testing N/A ✉

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*

ii. the plan for the collection of material or the conditions under which material will be received *Write here*

iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*

iv. the methods to uphold confidentiality *Write here*

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*

C. Is widespread sharing of materials planned? *Write here*
D. When and under what conditions will materials be stripped of all identifiers? *Write here*
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*

F. Describe the provisions for protection of participant privacy *Write here*
G. Describe the methods for the security of storage and sharing of materials *Write here*

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

The subject population for this project is adolescents between the ages of 16-19. Young adults aged 18-25 will be recruited for focus groups as well. There are also adults (19-80) that will be recruited to participate in separate focus groups at the Convention.

For this study, 8 focus groups of 5 adolescents each (n = 40), boys and girls in Connecticut, aged 16-19 will participate in the focus groups and 30 adolescents, boys and girls, aged 16-19 will participate in the pilot testing of the adapted game (2 groups of 3 adolescents will participate virtually and 6 groups of 4 adolescents each will participate in person at their school site while following COVID-19 guidelines). These adolescents will be recruited from the high schools that we already have established partnerships with, such as Maloney High and Hamden High. In addition, we will conduct 4 focus groups of young adults aged 18-25 (N=20) in Connecticut. These young adults will be recruited from local universities. Additionally, 30 youth (16-19) over the course of two years (e.g., meeting annually) from the national School-Based Health Alliance (SBHA) National Convention will also be recruited to participate in focus groups for the project.

For the focus groups with the adults, 50 adults (19-80) who are affiliates of the SBHA will be recruited over the course of two years (e.g., meeting annually) during the national SBHA Convention to participate in the project and will receive information sheets. Their role represents various positions within school-based health centers across the nation. Their role in this study is to be part of our focus groups to help inform game development and implementation strategies.

For the individual interviews, up to 20 participants aged 16-25 who are currently receiving treatment for opioid use disorder will be recruited to participate in this study. The Director of Research at the APT Foundation has approved and will post flyers (see example of the flyer attached) on site at the APT Foundation. Other interview participants may be recruited through provider referral. Interested participants will contact our research team to participate.

For interviews with treatment providers of opioid use disorder, up to 20 adults (19-80) who have treated individuals aged 16-35 for opioid use disorder within the last 5 years will be recruited. Clinical directors at each APT Foundation location will inform treatment providers about our study and other colleagues may be contacted via email and from snowball sampling from other providers that participate in the interviews. Interested participants will contact our research team to participate.

For focus groups with stakeholders (educators, prevention specialists, etc.), approximately 20 adults (19-80) will be recruited. Our team may collaborate with various organizations (e.g., FCD Prevention Works, First Book) to recruit participants. Interested participants will contact our research team to participate.

Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

181 Children	181 Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

   Adolescent participants must: 1) attend high school that has a school-based health center, and 2) be 16-19 years (grades 9-12) to participate in the game development focus groups or pilot testing OR they must be a member of the School-Based Health Association Youth Advisory Council to solely participate in the focus groups.

   Young adult game development focus group participants must be 18-25 years old.

   Adult participants that will be participating in focus groups during the game development phase must be national school-based health center personnel and be between the ages of 19-80.

   Interviews with individuals in treatment: Participants must be between the ages of 16-25, receiving treatment for an opioid use disorder, a device to access the internet for the virtual interview and be able to sit for 60-90 minutes in an interview.

   Treatment providers: Participants must be adults between the ages of 19-80, have provided medical treatment for individuals aged 16-35 in the last 5 years for opioid use disorder, a device to access to the internet for the virtual interview, and be able to sit for 60-90 minutes for an interview.

   Stakeholders: Participants must be between the ages of 19-80, qualify as a stakeholder in the project (e.g., an educator, prevention specialist, etc.), have access to a device to access the internet for a virtual focus group, and be able to sit for 60-90 minute for a focus group.

8. How will **eligibility** be determined, and by whom? Write here

   For youth focus groups & pilot study: In order to be eligible for either the youth focus groups or the pilot study, adolescent participants must: 1) attend a high school that has a school-based health center, 2) be 16-19 years (grades 9-12), and 3) coordinate reliable transportation home or to their next location. The research assistant (in collaboration with the designated school liaison/champion) will screen for eligibility and discuss the study with the participant and their parent/guardian.

   For young adult focus group participants: In order to be eligible for the young adult focus group the participant must be between the ages of 18-25.

   For adult focus groups: In order to be eligible for the adult focus group, the participant must be a school-based health center affiliate and between the ages of 19-80.

For the individual interviews with adolescents and young adults who are currently in treatment for opioid use disorder: Upon expressing interest, phone screens will be conducted by the research team to ensure eligibility. The phone screen will verify that the participant is between the ages of 16-25, receiving treatment for opioid use disorder, a device to access the internet for the virtual interview, and is able to sit for 60-90 minutes in an interview. Participants will be recruited through flyers posted at the APT Foundation as well as through provider referral. The purpose of this study will be to learn from their experiences and inform the content of the videogame intervention through their perspectives and stories from their view of the past to help build out an effective and relatable intervention.

For treatment providers: Upon expressing interest, phone/ email screens will be conducted by our research team to confirm that the individual is a treatment provider and has treated individuals aged 16-35 for opioid use disorder within the last 5 years. Participants will be recruited through clinical directors at their APT Foundation site as well as via email and from snowball sampling from other providers that participate in the interviews.. The purpose of this study will be to learn about their experiences treating individuals for opioid use disorder (OUD), any stories they are willing to share and their opinion on what should be included in a videogame that aims to prevention opioid misuse in adolescents.

For stakeholders: Upon expressing interest, our team will verify that the individual is aged 19-80 and holds a position that enables them to provide insight to our study (e.g. an educator to our target population, prevention specialist, etc.). Participants will be recruited through partnerships (FCD Prevention Works, First Book, etc.). The purpose of this study is to gather stakeholder's perspectives on what should be included in a game that aims to prevent opioid misuse in adolescents. In addition, we aim to learn development and implementation strategies.

Participation in this study will be strictly voluntary, confidential, and non-discriminatory. Participants will be enrolled either on-site or virtually during their first meeting. The study team will enroll adolescents, aged 16-19 years (grades 9-12) from schools with school-based health centers. In partnership with school-based health centers, we will provide flyers and announcements to the general population of students via school meetings and physical education/health classes. In collaboration with community program staff, we will discuss the study with interested adolescents and parents/guardians (for those participants ages 16-17) and collect eligibility screening data. In describing the study to the participant, the purpose of the study will be described as "finding out how kids can make choices and decisions that are healthier for them." It is important to note that this part of the study is NOT about engaging youth who already misuse opioids; the focus of this part of study is on prevention. In describing the study to the parent/guardian, we will indicate that the study will focus on promoting healthy behaviors in adolescents, and on providing strategies to assist adolescents in making decisions about the many challenges they face during adolescence, including the risks associated with drug misuse. If the participant is eligible and interested, we will proceed with the consent procedures. On separate occasions, we will give information sheets to the adolescents and to their parents describing the purpose of and protocol for the focus groups and pilot-testing depending on the stage of study. For participants under age 18, parents/guardians who do not wish for their teens to participate may contact the research staff for clarification on purpose and/or protocol. As we have done with all of our other HIC protocol, we will provide all of our focus group participants an information sheet and they may opt-out of them. No forms will be signed for focus group participation. Consent and assent documents will be signed for pilot study participation.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The potential risks associated with this study have to do with maintenance of the confidentiality of the identities of the participants enrolled in the study and information relating to them. As with all of our studies, we will train study researchers in maintaining confidentiality. Prior to the start of the focus group, researchers will discuss potential risks including breach of confidentiality. Examples include but are not limited to informing participants at the beginning of focus groups of risks related to confidentiality and the sensitive nature of the topic, by conducting focus groups in a private classroom in the school, by training and reviewing questions with our team of experts who specialize in addiction medicine, and by informing study participants via information sheets of the risks of confidentiality breaches. Discussion topics will focus on interested content to build out narratives for game development. Participants will be encouraged to only disclose what they are comfortable sharing and to consider sharing suggestions for building out a videogame intervention as opposed to confidential information about themselves. De-identified hard copies of any data will be stored in locked cabinets and electronic data will be stored in secure, password-protected computers. Only the PI and other relevant research staff will have access to the data.

Playing the ***PlaySmart*** game or engagement in discussions with the research team about its content may pose a potential psychological risk in that we address sensitive issues around drug use and its consequences. The research staff will be available to provide assistance to all participants, answer their questions, and serve as a resource if any distress or concern arises. The assessments and instruments may also present a potential risk given that some of the questions are sensitive in nature and address issues around drug use and risky behaviors. Again, the research staff will be available to assist the participants and the program site staff if there appears to be any distress around the questions being asked and connect them to appropriate school personnel.

If there are concerns about issues raised with regards to substance use or mental health, or if participants need additional or more intensive attention, the research staff will contact Dr. L. Fiellin or Dr. Fernandes (who is a Licensed Professional Counselor and has extensive expertise working with adolescents and schools) who will discuss providing further consultation to the participant.

It is anticipated that the adolescents enrolled in this study should benefit directly from the study as the purpose of the study is to facilitate increasing their perception of risk of harm from initiating the misuse of opioids, decreasing their actual misuse of opioids, as well as improving their decision making and knowledge to optimize their abilities to negotiate around risky behaviors. The potential benefits to participants are great while strict precautions are being taken to protect the confidentiality and well- being of participants, as has been described above. Thus, the potential benefits to the participants outweigh the potential risks.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

This study presents minimal risks to the participants and adverse events or other problems are not anticipated.

Adverse Events (AEs):
Violation of confidentiality: Any breach of confidentiality.
Discomfort due to assessment procedures: Discomfort created by answering survey questions.
Embarrassment in disclosing sensitive personal information.
Disclosure of information about current and/or intended physical harm to persons; current and/or intended abuse of children that would be reported to a child welfare agency; and/or an investigation of such allegations(s) that could ensue.
Dissatisfaction with the intervention activities: In this case it would be the game intervention. While gaming addiction is a recognized entity, it is very rare and, in the setting of playing a serious game, very unlikely. If there are any concerns of developing serious addictive behaviors in our pilot study participants, we have team members who are experts in the field of addiction medicine and will address these issues immediately.

Serious Adverse Events (SAEs):

SAEs include death, life threatening injury or condition, hospitalization, persistent or significant disability/incapacity, and other conditions which in the judgment of the investigators represent significant hazards. In the rare evident of an SAE, we do not expect them to be related to our study.

Procedures for research team management of AEs, SAEs and other study risks such as mandatory reporting requirements:

This study presents minimal risks to the participants and adverse events or other problems are not anticipated. In the unlikely event that such events occur, Reportable Adverse Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the IRB (using the appropriate forms from the website) and the NIDA PO. The PI will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings and via email as they are reviewed by the PI. We will use procedures to detect and respond to adverse events that ensure prompt discovery of any adverse events and to minimize their effects. There is adequate surveillance and protections to discover adverse events promptly and keep their effects minimal.

Procedures for training and supervision of all research personnel have been developed as part of our previous and current studies. All members of the research team are familiar with procedures for identifying and reporting possible adverse reactions. All members of the research team are trained in mandatory reporting and will notify the PI immediately of any concerns raised about participant mental health (suicidality), substance use, abuse of any kind, and so forth.

If an adverse event occurs study personnel will notify the PI as well as the appropriate Information Security Officer (ISO) and follow all necessary procedures. All adverse events are reported using the Yale Institutional Review Board (IRB) standard template for reporting adverse events. The PI reviews all adverse events, classifies the attribution of adverse events (e.g., definitely, probably, possibly related; unlikely or unrelated) and grades the severity of the event, utilizing the FDA's definition of serious adverse events, on a 6-point scale (0=no adverse event or within normal limit; 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal). Serious unanticipated or anticipated adverse events will be reported immediately to the IRB and to the NIDA PO within 24 hours by phone and/or email and will submit a written report to the PO no more than two days later. Adverse events will be reported in summary form at least annually to the IRB. The summary will include the number of participants enrolled and a summary of graded adverse events to date, using the chart format included in the Yale University DSMP template. The PI will evaluate all adverse events and determine whether the event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (e.g., Risks to Subjects) or consent form (e.g., Risks and Inconveniences) are required.

The PI will be responsible for monitoring the data and conducting performance and safety reviews, at the specified frequency. Either the PI or the IRB have the authority to stop or modify the study. The monitoring by the IRB will occur annually at the time of re-approval. The PI will conduct data and safety review at least quarterly and at any time a serious adverse event occurs. During the review process, the PI will evaluate whether the study should continue unchanged, requires modification or amendment to continue, or should be closed to enrollment.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this

study? Minimal risk

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? Minimal risk

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
   i. Minimal risk
   ii. Greater than minimal

Dr. Lynn Fiellin will not be involved with any participant recruitment and/or data management nor data analysis. Tyra Pendergrass Boomer is appointed as the co-investigator who will be independent of Dr. Fiellin's review over subject selection and adverse event reporting responsibilities.

We are in the process of establishing a Data and Safety Monitoring Board (DSMB) that will also be in place for the subsequent randomized controlled trial. The DSMB will be comprised of comprised of two experts in clinical trials in adolescents (one with expertise in substance use prevention) and an expert in statistical analysis of clinical trials and will provide oversight in a number of areas including for the selection, enrollment, or consenting of participants, or determination of eligibility.

d. For multi-site studies for which the Yale PI serves as the lead investigator:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   iii. What will the multi-site process be for protocol modifications? *Write here*

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Data analyses general considerations: Statistical procedures and models for analyzing data have been selected according to the research hypotheses and the types of data available. In general, we will use two- tailed tests and p-values smaller than 0.05 will be considered statistically significant. When necessary, we will adjust the level of significance (alpha) to account for multiple statistical tests. All statistical analyses will be conducted on an intention-to-treat sample using either SPSS or SAS statistical packages.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒ N

☐ ☐ ☐ ☐

B. DRUGS/BIOLOGICS ☒ N/

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☒ ☒ ☐ ☐

☒ N

B. DEVICES

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C::::::::J C::::::::J C::::::::J C::::::::J SECTIONIII: RECRUITMENT/CONSENTAND ASSENTPROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale forthisprotocol: 150

b. If thisis amulti-site study,givethetotalnumber of subjects targetedacross allsites: *Write here*

2.Indicate recruitment methodsbelow. Attach copiesof anyrecruitmentmaterialsthatwillbeused.

181 Flyers	☐InterneUwebpostings	D Radio
181 Posters	☐Massemail solicitation	☐Telephone
☐Letter	☐Departmental/Center website	D Television
☐Medical recordreview*	D Departmental/Centerresearchboards	D Newspaper
☐ Departmental/Centernewsletters	D Web-based clinical trial registries	D Clinicaltrails.gov
☐ YCCI Recruitment database	☐Social Media(Twitter/Facebook):	
181 Other: Meeting with school and program staff, school orientations andopenhouses,announcements in schools, also SBHA representative send emails to affiliates and YAC for the Convention		

* **Requests for medical records should be made through JDAT as described at** http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. *Write here*

b. Describe how potential subjects are contacted. *Write here*

Who is recruiting potential subjects? *Write here*

For game development focus groups, students will be recruited through flyers and announcements to the student general population via school meetings and physical education/health classes. Members of our team will also make lunchroom and classroom announcements about our project. We will also ask school teachers/administrators to share announcements about our study to their students. Potentially interested students will receive an information sheet describing the purpose of the research activity and they will be able to agree or decline.

For the young adult focus groups, participants will be recruited through flyers and announcements. Interested participants will be encouraged to contact our team through a number on the flyer. We will work with local universities to follow their protocols in recruiting participants from their school.

For National Youth Advisory Board focus groups, participants will be recruited through announcements and flyers (both via email) and working with School Based Health Alliance partners to identify potential participants who may serve as affiliates of school-based health centers by emailing the flyer via their listserv. Recruitment will consist of sending out flyers via email and making announcements via email to all involved in the Youth Advisory Council as well as making an announcement to those who are affiliated with the School-Based Health Alliance via the School-Based Health Alliance listserv before the Convention. Since the Youth Advisory Council is part of an existing council within the national organization, we will share the details of the study with this group

by working with the SBHA before the start of the Convention. A representative from the SBHA will email (see email in documents section) members of the Youth Advisory Council up to three times. In the first email, the representative will share details about the study and how to contact our team if one chooses to participate voluntarily. If study team is contacted, youth will provide verbal assent/consent over the phone. If youth are minors, it will be explicitly stated that parental/guardian verbal consent over the phone is required prior to participation. If email was sent three times and the person did not respond, our team will respect their wishes of not wanting to participate. The Youth Advisory Council is an established group that is part of the SBHA and, therefore, contact with parents/guardians is common for those who are minors. Potentially interested National Youth Advisory Board members will receive information sheets describing the purpose of the research activity and they will be able to agree or decline. Members of the National Youth Advisory Board consist of minors (younger than 18) in high school and adults (18 and older) in college. This is an established group and, therefore, those who volunteer to participate in our study will be contacted by email up to three times by a SBHA representative prior to the conference and, if interested in voluntary participation, parents/guardians will receive information sheets by mail or email for minors in the Youth Advisory Council.

For interviews conducted with participants aged 16-25 who are currently in treatment, we will post flyers at the APT Foundation where participants are able to contact a member of our research team if s/he is interested in participating in our research study. We will work with the APT Foundation to follow their strict research protocols in recruiting participants from the APT Foundation. In addition, providers can refer individuals that might be interested in participating in the interview;

For interviews with treatment providers, a member from our team will contact the clinical director of each APT site. The clinical director will then inform providers of the opportunity. Interested participants will contact a member of our team. We will work with the APT Foundation to follow their strict research protocols in recruiting participants from the APT Foundation. In addition, we will recruit via email and from snowball sampling from other providers that participate in the interviews to recruit those treatment providers that may not be associated with the APT Foundation.

For stakeholder focus groups, our team will work with organizations such as FCD Prevention Works and First Book to recruit participants for our study. Organization leaders will share information about the focus group opportunity to their contacts. Interested participants will contact a member of our team.

Recruitment/enrollment and conduct of this pilot study will be in collaboration with the school-based health center at one Connecticut high school where there is a high prevalence of high-risk adolescents and where we already have developed a partnership. The **recruitment plan** will replicate similar plans conducted in the last 10 years at our lab around sensitive data. They include recruitment via flyers and announcements at the school. As we have done with other studies, examples include providing announcements to teachers/staff to share in classrooms, introductions during classes, and providing information about the study to all interested students during lunch. Flyers and information will highlight this is a research study developing and evaluating a digital intervention for substance use prevention and to help adolescents make better healthier decisions.

Additionally, we will also recruit adult participants from the annual School-Based Health Alliance Annual Convention to participate in focus groups and/or interviews. Adult participants represent a sample of school-based health centers across the nation. Potentially interested affiliates/attendees will receive information sheets describing the purpose of the research activity and they will be able to agree or decline.

The research study team will carry out all recruitment procedures.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

DoestheInvestigator oranymember oftheresearchteamhavea directexistingclinicalrelationship withany potential subject?
o Yes, allsubjects
o Yes, some of the subjects
rgJNo

If yes, describe the nature of this relationship. *Write here*

5. **Request forwaiver ofHIPAA authorization:**(WhenrequestingawaiverofHIPAA Authorizationforeitherthe entirestudy,orforrecruitmentpurposesonly. Note:ifyouarecollectingPHIaspartofaphoneoremail screen, you must request a HIPAA waiver for recruitment purposes.)
Choose one:
181For entire studyfor focus groups (includingtelephone screeningwhenverbal authorization willbeobtained, and later subject will be consented verbally.
181 For recruitment/screening purposes only for pilot group
□ Forinclusionofnon-Englishspeakingsubjectif shortformisbeingusedandthereisnotranslated HIPAA research authorization formavailableontheUniversity'sHIPAAwebsiteat hipaa.yale.edu.

   i. Describe whyitwouldbeimpracticable toobtainthesubject'sauthorization foruse/disclosureofthis data: only waiver of signed authorization is requested

   ii. Ifrequestingawaiverof**signed**authorization,describe why it would beimpracticabletoobtainthe subject's signed authorization for use/disclosure ofthisdata:phone screen for potential subjects, focus group will be verbally consented.

Theinvestigator assuresthattheprotectedhealthinformation forwhicha Waiver ofAuthorization hasbeen requestedwillnotbereusedordisclosedtoanypersonorentityotherthanthoselistedinthisapplication, except asrequiredbylaw, forauthorized oversight ofthisresearchstudy, orasspecifically approvedforuseinanother study by anIRB.

Researchers are*reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entitymust beaccounted forinthe"accountingfordisclosures log", bysubject name, purpose,date, recipients, andadescriptionofinformationprovided. LogsaretobeforwardedtotheDeputyHIPAAPrivacy Officer.*

6. **Process of Consent/Assent:**Describethe settingandconditions under whichconsent/assentwillbeobtained, includingparentalpermissionor surrogatepermissionandthestepstakentoensuresubjects'independent decision-making.

Screening and consent:

For the pilot RCT: The research assistant (in collaboration with the designated school liaison/champion) will screen for eligibility, discuss the study with the participant and their parent/guardian, and obtain informed written assent from the individual and written informed consent from their parent/guardian (if under age 18). Participants will be provided with an age-appropriate description of the study as "finding out how teens can make choices that are healthier for them." In describing the study to the parent/guardian, we will indicate that the study is about promoting healthy behaviors and onproviding strategies to assist adolescents in making decisions about the challenges they face, including the risk for initiating drug use. If an individual or their parent/guardian indicates that they do not wish to participate, there will be no further involvement in the study. In the case of those participants who are over the age of 18 (18-19 years old) or are emancipated minors, we will obtain written informed consent from them.

Given the proposed study includes adolescent youth, we will be required in situations such as this to report any concerns that arise at the school as part of required mandatory reporting (all members of the research team have completed mandatory reporter training). This includes mandatory reporting for abuse and neglect to appropriate officials via Careline at 1-800-842-2288. Suicidal risk will be reported to school official as well as parent/guardian. In extreme cases, 9-1-1 will be called. Fortunately, we will be working closely with the personnel of the school-based health center who are well-trained in managing these types of situations. We will employ all necessary measures for protecting the confidentiality of our participants who agree to be in this pilot study.

Participants in the young adult focus groups an will be over the age of 18 and will provide verbal consent before the group commences.

For the interviews with individuals in treatment for Opioid Use Disorder: Individuals who express interest in being interviewed (via text, email and/or a phone call) will schedule a brief phone call screening with a research assistant who is a member of our research team. During the phone call, the research assistant will verify that the individual meets eligibility criteria (e.g., between the ages of 16-25, receiving treatment for an opioid use disorder, a device to access the internet for the virtual interview and be able to sit for 60-90 minutes in an interview). If the individual meets this criteria and is a minor, our team will request parent/guardian contact information at the conclusion of the screening call in order to obtain parental/guardian consent from individuals between 16-17 before scheduling an interview. With their parent/guardian contact information, a member of our research team will schedule a phone call with a parent/guardian to describe the study. We will then provide an electronic version of the parent/guardian consent to the parent/guardian. Once we receive the appropriate signature, we will schedule an interview with the minor. If the individual is aged 18-25, an interview will be scheduled with them immediately after the screening portion of the phone call.

For interviews with treatment: Individuals will express interest in being interviewed to our team via text, email, or phone call. A research assistant from our team will screen the potential participant via a brief phone call or email. The research assistant will verify that the interested individual is a treatment provider, and they have treated individuals aged 16-35 for opioid use disorder in the last 5 years. If the individual meets this criteria, they will then be scheduled for a virtual interview with our research team. Our team will ensure that the participant has access to internet and an appropriate device.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   This research does not involve subjects with limited decision-making capacity. Parents and adolescents will be provided with an age-appropriate description of the study and told about what they might expect. In describing the study to the participant, the purpose of the study will be described as "finding out how kids can make choices that are healthier for them". In describing the study to the guardian/parent, we will indicate that the study will focus on promoting healthy behaviors in adolescence and on providing strategies to assist adolescents in making decisions about the many challenges they face, including risk for initiating drug use. For focus groups, we will employ information sheets. Parents who do not wish for their children to participate may contact the project director. For pilot-testing, we will obtain informed written assent from the participant and written informed consent from their guardian/parent.

8. **Non-English-SpeakingSubjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Non-English-Speaking Subjects will not be included to participate in this study.

Asa limitedalternativeto the aboverequirement,willyouusetheshortform*forconsenting processifyou unexpectedly encounteranon-Englishspeaking individualinterestedin study participationand thetranslation of the longform is not possible prior to intended enrollment? YES D NOD

- Ifmorethan2 studyparticipants areenrolledusing a shortformtranslated intothesamelanguage,then thefullconsentformshouldbetranslatedintothatlanguageforusethenexttimeasubjectspeakingthat language is to be enrolled.

Severaltranslated shortformtemplates areavailableontheHRPPwebsite(yale.edu/hrpp) andtranslated HIPAA ResearchAuthorization Forms areavailableontheHIPAAwebsite(hipaa.yale.edu).Ifthetranslation oftheshort form isnotavailableonourwebsite, then thetranslated shortform needstobesubmittedtothelRBofficefor approvalviamodificationpriortoenrollingthesubject. ***Pleasereviewtheguidanceandpresentationonuseof the short form available on the HRPP website.***

Ifusing a short formwithout a translated HIPAA Research Authorization Form, pleaserequest a HIPAA waiver in the section above.

9. ConsentWaiver: Incertaincircumstances,theHICmaygrantawaiverofsignedconsent,orafullwaiver of consent, depending onthestudy. If youwillrequest eithera waiverof consent,orawaiver ofsignedconsent for this study, complete the appropriate section below.

☐ **Not Requesting any consent waivers**

r::::::liEiilli: Requesting a waiver of signed consent:

Recruitment/Screeningonly*(ifforrecruitment, thequestions intheboxbelowwillapply to recruitmentactivities only) telephone screen for all groups*

Entire Study (Note thatan informationsheet may berequired.) for entire study requesting waiver of signedconsent for focus groups and1reanet ileveA-Sthatwill use verbal consent. However, signed consent will be collected during the pilot phase.

For a waiver of signed consent, address the following:

- Wouldthesignedconsentformbetheonlyrecordlinkingthesubjectandtheresearch? **YESDNOD**
- Doesabreachofconfidentialityconstitutethe principalrisktosubjects? **YES☐NOD**

OR

- Does the research pose greater than minimalrisk? **YES DN0181**
- Doestheresearchincludeanyactivitiesthatwouldrequire signedconsentina non-researchcontext?YES☐

☐ **Requesting a waiver of consent:**

D **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activitiesonly)*

Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  - D Yes *If* ***youanswered yes, stop. A waivercannotbe granted.***
  - D **No**
- Will the waiver adversely affect subjects' rights and welfare? **YES ☐NOD**
- Why would the research be impracticable to conductwithout the waiver? *Write here*
- Whereappropriate,howwillpertinentinformationbereturnedto,orsharedwithsubjectsatalaterdate? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. Whatprotectedhealth information (medicalinformationalong withtheHIPAA identifiers) about subjectswill be collected and used for the research?

   Names, phone numbers, addresses, email addresses, parenVguardian names, parenVguardian phone numbers, and parent email addresses will all be collected.
2. How will the research data be collected, recorded and stored? *Write here*

A web-based computer system (Redcap) will be used for data collection, management, and monitoring. The web-based data system Clinical Trial Management System (CTMS) is under the auspices of the Yale Center for Medical Informatics who is responsible for data management. It is a web-accessible, multi-disciplinary database for study- or disease-specific clinical research data designed to store the focused data required for clinical trials and clinical research studies. This system has proven to be very efficient and reliable in other clinical trials. It will be used by the research assistant to administer the research instruments from any computer with Internet access. The CTMS will be used to generate a number of web accessible reports and reminders to help monitor and manage the data collection process to assure completeness of evaluation. The system can check for data inconsistencies, omissions, and errors regularly. Data questions or problems will trigger data queries and analyses of missing data will be done periodically to assure that all forms are entered and available for analysis. CTMS staff have received HIPAA training and Human Subjects Protection training. Users will certify that they are HIPAA trained and will act in full compliance of HIPAA regulations. Specifically, individual profile data and data on application use by study participants will be collected and de-identified through irreversible hashing methods prior to storage to ensure privacy protection is satisfied. De-identified data will be encrypted in transit and securely transferred for storage and analyses.

The web data-entry interface allows data entry to be performed from anywhere on the Internet and uses 128-bit secure sockets layer security to protect the confidentiality of the data. The CTMS maintains an electronic audit trail of all modifications to a study's data, including the user who made the change, date and time, each data item changed and its previous value and new value. Yale houses and maintains the security and backup of all servers and workstations. The CTMS's Oracle database is housed in a central machine room maintained by Yale. Passwords and subject identifying data will be stored encrypted in the database server. Several levels of database backup are performed regularly, including full daily and incremental backup.

Data Collection from Videogame Software Procedures:

In our other web-based videogame studies we collect in-game data through our secured online

server.

We have developed a system for collecting, securing, and storing gameplay data (both **Player Game State Data** and **Activity Logging Data)** that will be used for the proposed pilot study. Player Game State Data allows us to monitor the progression of the player through the game. The Activity Logging Data allows us to see the decisions the player makes throughout the game. This system is outlined here:

1. After receiving an unidentifiable, unique User ID and password from the research staff, each player logs in to the web-based game through a Chrome or Safari web browser on an iPad. The game is accessible only through our secured online server.
2. During each game play session, **Player Game State Data** and **Activity Logging Data** is automatically collected within the game and is exported and stored on the secured online server. Data will not be collected or stored locally on iPads and will only be accessible from the secured online server, which will be password protected and only accessible by the research staff.
3. After each session is completed, the research staff will ensure each player is logged out oftheir unique game, will generate specific log files for each unique playsession.
4. The data will remain on the secured online server until all player game play sessions are complete, at which time the players' data will be downloaded as a single .csv file for optimization reasons and transferred securely to the Yale shared drive until the time data analysis isinitiated.

Videogame data collection security:

Personal identifying information is never kept on the secured online server and care is taken to ensure that none of the game data is put at unnecessary risk of being distributed to unauthorized people. iPads will always be in the possession of authorized personnel and locked in safes designed for iPads when not in use or in the possession of study participants (players) under the supervision of authorized personnel. **Player Game State Data** and **Activity Logging Data** are stored as unencrypted plaintext data. At the end of all players' game play sessions, data will be transferred over Yale's secure network, and not on the public Internet. The saved game data files belong to Yale and are only accessible by study personnel.

Data entry methods:

All data is entered by the research assistant or by the participant with research assistant supervision if needed. All data is entered directly into the web-based computer system, Redcap. All data entry will be completed with assigned ID numbers only. The research team regularly and systematically double-checks and confirms the completeness of data entry.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard DriveSecured Server ☐ Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security ofthe identifiable study data and the storage media indicated above during and after the subject's participation in the study?

Quality assurance plan (checks for errors):

The organizational structure used to ensure quality of data in this project include: 1) Extensive training and close supervision of research personnel in data collection and management; 2) Preliminary review of all data for completeness and coding errors by data manager/analyst; and

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3) Utilization of error-checking statistical procedures. The PI supervises data procedures. All error corrections are fully documented in the research records of the study. All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research. In addition, the Clinical Trials Management System (CTMS) will be used to generate a number of web accessible reports and reminders to help monitor and manage the data collection process to assure completeness of evaluation. The system can check for data inconsistencies, omissions, and errors regularly.

Procedures for preventing and addressing breaches of confidentiality:

One of the potential risks associated with this study pertains to the maintenance of the confidentiality of the identities of the participants enrolled in the study and information relating to them. De-identified hard copies of the data will be stored in locked cabinets and electronic data will be stored in secure, password-protected computers. Only the PI and other relevant research staff will have access to the data.

A number of precautions will be actively integrated into the research procedures to protect the confidentiality and anonymity of all participants. As we have done with our other videogame intervention studies, a Certificate of Confidentiality will be automatically provided by the National Institute on Drug Abuse upon their granting the award. All research staff participating in the study will be required to complete training in research ethics. Data collection forms will be designated by ID numbers only. A separate master file of names, addresses, contact persons, and telephone numbers, along with the study ID numbers will be maintained in a locked file cabinet in the PI's research offices. All data entry and analyses will be completed with ID numbers only. The study will be explained to others, such as the parent/guardian and program staff as a study of child development that will focus on promoting healthy behaviors. In instances in which data are requested from other sources or it is beneficial to the participant to provide information to another individual or agency (e.g. medical personnel) this will only be done with the written permission of the parent/guardian on a "Release of Information" form stipulating who the information is provided to, or received from. The research staff will follow standard confidentiality procedures for research programs.

Any breaches of confidentiality will be reported immediately to the participant, their family, and relevant school personnel as well as the IRB and the NIDA PO as well as the HIPAA Privacy officer. Additional systems will then be instituted to prevent a similar breach from occurring.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

   Data collected in the study will reside in our computerized database and electronic storage mechanisms. All data analyses will be performed under approved HIC protocols.

   If appropriate, has a Certificate of Confidentiality been obtained? Following newguidelines enacted in 2017, the NIDA/NIH will automatically grant a COC for this project.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to thesubject(s)or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

It is anticipated that the young adolescents enrolled in this study should benefit directly from the study as the purpose of the study is to improve their attitudes, intentions, and knowledge, and decision-making around health promotion and opioid use. This research has the potential to benefit a large number of youth around the country and worldwide, because if in the pilot test the intervention is shown to be effective, then this intervention can be replicated elsewhere and with a greater ease of dissemination. The potential benefits to participants are great and strict precautions are being taken to protect the confidentiality and well-being of participants, as has been described above. Thus, the potential benefits to the participants outweigh the potential risks.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   No participation in the study

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Each participant (adolescents and young adults) will receive a $30 gift card for participating in the game development focus group.

   Each participant will receive a $30 gift card for participating in the individual interviews conducted with adolescents and young adults who are currently in treatment for opioid use disorder.

   Each participant will receive a $30 gift card for participating in the individual interviews conducted with treatment providers who have treated individuals 16-35 for opioid use disorder in the last 5 years.

   Participants in the pilot study will either receive a $25 gift card for one two-hour gameplay session and follow-up questions (in person) OR two gift cards totaling $60 for six one hour gameplay sessions and follow-up questions (virtually).

   Focus group participants from the national Youth Advisory group will receive $35 for their participation. Because this will be happening during a conference, we added a $5 incentive to participate in the focus group.

   School-based health center affiliates will receive $35 for participation in their respective focus group. Because this will be happening during a conference, we added a $5 incentive to participate in the focus group.

   Stakeholder focus group participants will receive a $30 Visa gift card for their participation.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

No costs to participants will be incurred for participating in any part of this study.

In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research

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thatpresentsthepotential forphysicalharm(e.g.,researchinvolving blood draws).

All study related procedures do not involve any physical activity other than discussion and use of a device (e.g., iPad, phone, and/or computer.)

a. Will medical treatment be available if research-related injury occurs? *Write here*
b. Where and from whom may treatment be obtained? *Write here*
c. Are there any limits to the treatment being provided? *Write here*
d. Who will pay for this treatment? *Write here*

How will the medical treatment be accessed by subjects? *Write here*

IMPORTANT REMINDERS

Will this study have a bill able service?Yes☐ **No181**

Abillableserviceisdefinedasanyserviceenderedtoastudysubjectthat,ifhelshewasnotonastudy,would normally generateabillfromeitherYale-NewHavenHospitalorYaleMedicalGrouptothepatientorthepatient's insurer.Theservicemayormaynotbeperformedbytheresearchstaffonyourstudy,butmaybeprovidedby professionalswithineitherYale-New HavenHospitalorYaleMedicalGroup(examplesincludex-rays,MRIs,CT scans,specimenssenttocentrallabs,orspecimenssenttopathology).Notes:1.Thereisnodistinctionmade whether theserviceispaidforbythesubjectortheirinsurance(Standard ofCare)orbythestudy'sfunding mechanism(ResearchSponsored). 2.Thisgenerallyincludesnewservicesorordersplacedin EPICforresearch subjects.

Ifanswered,"yes",thisstudy willneed tobe setupin OnCore,Yale'sclinical researchmanagement system,for Epictoappropriatelyrouteresearchrelatedcharges.Pleasecontactoncore.support@yale.edu

Arethereanyproceduresinvolvedinthisprotocolthatwillbeperformedat YNHHoroneofitsaffiliatedentities?

Yes☐No CB:I

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

Yes☐No

D

b. Will you be using any new equipment or equipment that have not used in thepast for tsprocedure?

Yes

D **No☐**

c. Will a novel approach using existing equipment be applied? **Yes ☐No☐**

If youanswered "no"to question 4a,or"yes"toquestion4borc,please contactthe YNHHDepartment of Physician Services(688-2615)forpriorapprovalbeforecommencingwithyourresearchprotocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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