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Title: "An Accessible Digital Intervention to Promote the use of school-based health centers and to empower adolescents with their sexual health"

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Protocol Title: "An Accessible Digital Intervention to Promote the use of school-based health centers and to empower adolescents with their sexual health"
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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.

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SECTION I: RESEARCH PLAN

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

In 2009, 39% of new HIV infections occurred among individuals 13–29 years old, a 21% increase in incidence since 2006[1]. Notably, undiagnosed HIV cases are thought to be highest among youth and young adults. The U.S. Centers for Disease Control and Prevention (CDC) estimate that more than half of all undiagnosed HIV infections are in youth aged 13-24 years[2]. Although HIV testing is widely available, self-reported rates of HIV testing have not changed[3]. While 46% of high school students have had sex at least once, only 13% report ever having had an HIV test [4,5].

Given that adolescents are at such high risk, it is critical to give them the information, motivation, and skills to get HIV testing and counseling (HTC), helping them to minimize their risk and maintain their uninfected status. The current proposal focuses on adapting an existing HIV prevention videogame, PlayForward: Elm City Stories (R01HD062080), developed for 11-14 year olds, to include a primary focus on promoting access to and uptake of HTC in adolescent boys and girls, ages 15-18. PlayForward, an engaging and interactive videogame grounded in social learning theory and the theory of planned behavior, was developed through extensive work with its target audience to focus on the delay of sexual initiation in young teens and is currently demonstrating preliminary efficacy in a large randomized controlled trial (RCT). In Phase I for this protocol, PlayForward will be adapted for use in a slightly older age group with the primary outcome of encouraging them (increasing intentions) to obtain HTC as an important mediator of engaging in HTC[6], as well as affecting actual rates of HTC and increasing knowledge about HIV/AIDS.

Using a videogame as the delivery method of this intervention is advantageous because it meets adolescents "where they are at." Traditional videogame play is frequent in adolescents; boys and girls from all backgrounds play them[7]. Additionally, "serious games," defined as games for a primary purpose other than pure entertainment, have been developed by our group and others to promote healthy behaviors in this age group[8-10]. There is also compelling evidence that "serious" videogames can have a role in health promotion and behavior change[8]. An interactive videogame is an ideal prevention platform, facilitating salient opportunities to engage in repetitive interactions to acquire and rehearse new skills that can transfer to real-life situations[11,12]. It has the capacity to reach a larger population, ensure more consistent fidelity to the intervention, and facilitate easier dissemination than other delivery methods.

In Phase I of this protocol, we build on the considerable work we have accomplished with the parent grant (R01 HD062080, PI: L.E. Fiellin). Working with the multi-disciplinary team of the play2PREVENT (p2P) Lab, we will conduct the formative work with our target audience and content experts to modify PlayForward for a focus on promoting HTC. We will refine the conceptual model we developed in the earlier project[13] to promote HTC using constructs from the theory of planned behavior, social learning and self-efficacy theories[14,15], and principles from message framing[16] grounded in prospect theory[17].

To this end, our specific aims for Phase I of this protocol targeting HTC in 15-18 year old adolescents are to:

Aim 1: Translate our culturally and socially-tailored videogame PlayForward to focus on HTC in an older age group of 15-18 year old boys and girls by:
a. Developing a conceptual model of the theoretical mechanisms of behavior change to be applied specifically within the game. We will develop this model with input from 4 focus groups of 5 adolescents each (n = 20, aged 15-18) and the extant literature.
b. Informing the development of a set of intervention manuals ("Game Playbooks") targeting the new outcome.

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Aim 2: Modify aspects of the PlayForward game to reflect this new focus by pilot testing it with 30 adolescents, aged 15-18 to determine in a pre-post design:
c. The intervention's acceptability and feasibility using self-report data on the game play experience.
d. Preliminary evidence of the efficacy of the intervention by collecting data on i) intentions to seek HTC; ii) actual obtaining of HTC; and iii) knowledge about HIV/AIDS.

Phase I of this protocol will serve as the foundation for a subsequent Phase II that will undertake full development of the proposed game with the potential of impacting the health and future of adolescents by increasing rates of HIV testing and counseling in a manner that is engaging and compelling and holds the promise of significant reach, dissemination, and impact.

The **specific aims** for Phase II of this protocol are to:

Aim 3: Further adapt and expand our culturally and socially-tailored videogame ***PlayTest!*** to have a greater focus on HTC in addition to HIV prevention in an older age group of 14-18 year old boys and girls by:

a. Refining our conceptual model of the theoretical mechanisms of behavior change to be applied specifically within the game. We will create new content with additional input from 4 focus groups of 5 adolescents each (n = 20, aged 14-18) and have them play-test the game.

b. This model will inform new intervention manuals ("Game Playbooks") targeting these new outcomes.

c. Building the new content from our focus groups into the game to adapt and expand its scope.

Aim 4: Establish a system for the newly adapted game for web access/distribution and program integration. We will continue to work with our commercialization partners on widespread distribution of the adapted game.

Aim 5: Conduct a randomized controlled trial in 296 adolescents (aged 14-18) to evaluate the acceptability and efficacy of the adapted game on its new web-based platform compared with a set of control games. We will measure outcomes such as rates of HTC, attitudes, perceptions, intentions, self-efficacy, and knowledge of HTC at baseline, six weeks, and three and six months. Phase II of this protocol will undertake full development of the proposed game with the potential of impacting the health and future of adolescents by increasing rates of HTC and HIV prevention in an engaging and compelling manner and holds the promise of significant reach, dissemination, and impact through implementation and commercialization.

Additionally, with permission from the parents we will photograph the teens during focus groups and game play sessions. These photos will be used on our website, www.play2PREVENT.org, foragirl.com and related social media accounts (Twitter, Facebook, etc) and for other purposes related to this study.

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

The overall proposed study will be conducted over a three-year period. Phase I will take approximately one year, while Phase II will take an additional two years. Phase I of this protocol will be conducted over a six-month period. During months 1-3, we will collect data necessary for game adaptation from our target audience. We will refine our logic model[13] for the proposed game with input from 4 focus groups of 5 adolescents each (n = 20), aged 15-18, and create a series of behavior change gameplay manuals ("Game Playbooks"[85]) and storyboards (Aim 1). During months 4-6, we will adapt key components of the current PlayForward game on the iPad tablet to focus on HTC in boys and girls (yielding the new game PlayTest!), aged 15-18. We will pilot test it with 30

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adolescents, aged 15-18 to determine in a pre-post design the intervention's acceptability and feasibility using self-report data on the game play experience and collect preliminary data on the efficacy of the intervention in terms of intentions to seek HTC, actual HTC, and knowledge about HIV/AIDS (Aim 2).

Phase II of this protocol will be comprised of both a parallel and sequential set of processes between the play2PREVENT and Schell Games teams. In Stage 1 of Phase II, we will collect additional data for game adaptation from our target audience. We will refine our logic model[12] for the proposed game with input from 4 focus groups of 5 adolescents each (n = 20), aged 14-18 (months 1-4), and expand on our behavior change gameplay manuals ("Game Playbooks"[93]) (months 3-4). Our goal will be to create new content for Schell Games to incorporate into 2-3 new mini-games (skill-based games incorporated into the overall larger game). We will also make relevant modifications to 2-3 of the stories of the narrative focused specifically on HTC (months 3-8) (Aim 3). In this stage, Schell Games will establish the system to optimize the new adapted game for web access and distribution including generating the appropriate code, adding game player profiles, inputting the appropriate program hooks for analytics, and testing for quality assurance. At the same time, the Yale team will continue to work with their implementation and commercialization partners such as Peer Health Exchange (PHE) and MDR to further execute strategies for widespread distribution of the adapted game (months 3-8) (Aim 4).

In Stage 2 of Phase II, we will conduct a randomized controlled trial to evaluate the efficacy of the adapted game (*PlayTest!)* on its new web-based platform, comparing the adapted game with a set of control games with participants playing up to 12 hours of their assigned game(s) over six weeks. We will focus on outcomes around participants engaging in HTC, attitudes, intentions, and knowledge about HTC (months 9-24) (Aim 5).

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.

HIV incidence is high in adolescents, but rates of HIV testing and counseling are unacceptably low. Efforts targeting HIV prevention and care directed at youth and young adults critically lag behind that of adults[18]. Adolescents worldwide are less likely than adults to be tested for HIV, which can result in a late diagnosis and less effective care for infected individuals[19]. Barriers to HTC, particularly in adolescents, include potential disruption of education, fear of stigma and rejection, lack of access to testing sites, the lack of youth-friendly clinics[20], and a misunderstanding of testing policies[19]. An individual's perception of their own HIV risk can be significantly and inversely associated with their likelihood of engaging in sexual risk behaviors. One study of youth found that 80% of those who reported engaging in risky sexual behaviors felt they were not personally at risk for HIV[21].

Adolescence is an optimal developmental stage to target risk behavior change as it is a stage of heightened reward sensitivity and risk-taking[22] when decision-making skills are developed. There is a delay in the development of the pre-frontal cortex, and adolescents' knowledge of consequences is over-powered by perceptions of rewards in the limbic system, particularly social rewards[23-25,26]. It is a period of rapid physical and sexual development, and, therefore, presents a prime opportunity to address sensation-seeking and sexual experiences. In addition, this is a period of significant social and emotional development in which young teens increasingly focus on their interactions with others[27], an aspect that is key to videogame play with its interactive virtual characters. In addition, adolescents have documented low rates of health promoting behaviors such as HTC in the face of high rates of risk behaviors. These findings make our study cohort an ideal group to target with a videogame intervention for guidance and input on how to make decisions, reduce their risk, and more readily engage in health promotion behaviors.

The demonstrated lack of testing suggests that adolescents are not linked with appropriate treatment or preventive services, which can have dire consequences in terms of their overall health[19]. In addition to the behavior change theories that serve as the foundation of the videogame intervention, one of the strategies to increase HTC will be based on the concept of providing incentives within the game for the participant to access

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HTC. It has been proposed that the offer of incentives provides an "excuse" for HTC rather than the individual having to disclose their concern about their risk of infection. Further, through play, players will become more literate about key ways that their perceptions of their own HIV risk and HIV stigma impact their likelihood to get HTC. In a subsequent Phase II application, we will target some of the other barriers by creating a youth-friendly linkage[28] through the game to community sites, such as school health clinics, in order to access HTC.

Videogames are prevalent and promote health but have not focused on HTC. Ninety-nine percent of teenage boys and 94% of teenage girls, including all racial/ethnic groups, play videogames[7,29], and most play at least one hour per day[30]. Videogames have a well-established role in education because simulated role-playing is a highly effective approach for situated learning[31,32]. Active participation through simulated role-playing allows individuals to practice behavioral change in a safe and entertaining way[33,34]. In addition, research has shown that role-playing is a powerful strategy to influence attitudes[35,36]. Videogame interventions have demonstrated efficacy in affecting behaviors related to health promotion and disease management[8] in areas such as depression[37], asthma[33,38,39], diabetes[40,41], cystic fibrosis[42], cancer[12], and nutrition[11]. Accordingly, the fields of "serious games" and "games for health" are rapidly evolving[43,44]. There is also compelling evidence that individuals who acquire new information, motivation, skills, and behaviors in a virtual environment and then subsequently practice those entities in a virtual reality game are more likely to act in accordance with the new skills in real life[45,46]. To date, these games have targeted other conditions or situations but have not focused on HTC.
PlayForward is an evidence-based videogame intervention focused on risk reduction and HIV prevention in adolescents, with a primary focus on reducing sexual risk. It incorporates known theoretical constructs into a videogame context. The theoretical constructs underlying the current PlayForward game center on components from social learning theory and self-efficacy1[4,15,47]. Social learning theory and the concept of self-efficacy are proven elements found in positive youth and social development, sexual risk behavior programs, and HIV prevention programs. Social learning theory views learning as a dynamic interplay among personal factors (e.g., self-efficacy, intentions, and knowledge), environmental factors (e.g., social norms, parental influence), and behavioral factors (e.g., skills, practice). Many efficacious behavioral interventions focused on HIV and based on social learning theory and self-efficacy have targeted prevention in adolescents[48-52]. Self-efficacy is increased through acquisition of knowledge, translating knowledge into preventive action, having opportunities to practice the skills, and receiving the corrective feedback for targeted change[53]. A meta-analysis of interactive health communication applications demonstrated that interactive videogames improved self-efficacy[54]. PlayForward operationalizes the theory of self-efficacy with the player negotiating situations and practicing skills with the goal of promoting health behaviors and avoiding or reducing HIV risk behaviors.

In order to include a central focus on HTC, the adaptation of the current videogame will be guided by constructs from the theory of planned behavior that are already incorporated into the current PlayForward game[55]. The theory of planned behavior posits that intentions are the most proximal predictor of behavior, and there are a number of studies in the area of HIV risk and prevention that support this finding. Indeed, there is compelling evidence demonstrating that intentions to get HIV tested are a strong predictor of actual and subsequent behaviors[56,57 58,59]. Finally, in developing PlayForward, we used principles from message framing[16], which is grounded in prospect theory[60,61], as a mechanism for change in the target behaviors. Because the frame of a health message or decision point influences an individual's willingness to incur risk either to avoid an unwanted outcome or to encourage a desired one, messages embedded throughout the game will be systematically and strategically framed to provide relevant information as well as encourage the adoption of specific motivation and targeted health behaviors, including HTC[62].

The significant impact of an effective engaging videogame promoting HTC in teens (?)
In developing PlayForward, we incorporated the core efficacious elements of well-established HIV prevention interventions into the new delivery vehicle of an interactive game: 1) establish a framework to understand behavior change; 2) convey issue-specific and population-specific information necessary for healthy actions; 3) build cognitive, affective, and behavioral self-management skills; 4) address environmental barriers to implementing health behaviors; and (5) provide tools to develop ongoing social and community support for healthy actions. In this type of behavior change intervention, the delivery vehicle can be essential in terms of its ability to promote both beneficial and sustainable changes over time[87]. The proposed adapted version of

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PlayForward will seek to increase intentions to get HTC, increase rates of HTC, and increase HIV/AIDS knowledge in this older group of adolescents, aged 14-18.

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.

Overview of study design for Phase I

Phase I of the proposed study will be conducted over a six-month period. During months 1-3, we will collect data necessary for game adaptation from our target audience. We will refine our logic model[13] for the proposed game with input from 4 focus groups of 5 adolescents each (n = 20), aged 15-18, and create a series of behavior change gameplay manuals ("Game Playbooks"[85]) and storyboards (Aim 1). During months 4-6, we will adapt key components of the current PlayForward game on the iPad tablet to focus on HTC in boys and girls (yielding the new game PlayTest!), aged 15-18. We will pilot test it with 30 adolescents, aged 15-18 to determine in a pre-post design the intervention's acceptability and feasibility using self-report data on the game play experience and collect preliminary data on the efficacy of the intervention in terms of intentions to seek HTC, actual HTC, and knowledge about HIV/AIDS (Aim 2). Given our team's experience conducting this type of formative work and pilot testing, we are confident that this timeline is feasible.

Study sites: Recruitment/enrollment and conduct of this study will take place at one of the community high school programs with which we already have partnerships (e.g., Wilbur Cross High School; see Letter of Support). Our team has a consistent presence onsite and now has close working relationships with the program staff that are fully engaged in the recruitment process.

Procedures and design

Stage 1: Preliminary videogame adaptation

Conduct focus groups (4 focus groups of 5 adolescents each):

Two researchers will conduct focus groups according to standard procedures[90], utilizing a semi- structured interview method. In this method we will have a standard list of open-ended focus group questions to help promote discussion among the adolescents, but will ask additional follow-up questions not on the list to engage the adolescents in whatever topics and conversations may come about naturally during the focus group. We anticipate that 4 focus groups will be adequate to achieve thematic saturation[91]. Examples of potential focus group questions are: "What things worry you about getting tested for HIV?" and "What might help with this?" and "Who do kids turn to for advice or support?" In addition to asking adolescents open-ended questions, we will use creative methods (e.g., art projects, photograph activities, and storytelling) to promote discussion with the adolescents. During the focus group adolescent participants will be asked to use ~~a~~ pseudo (false) names. The facilitator will remind them ~~he/she~~ about this. We will audiotape this discussion so that we are able to use the information they and others in the group share with us for the development of the videogame. No identifying information will be collected. Instead, a study number will be used to identify them in audiotapes and other materials. If a participant does not wish to be audiotaped, then they will not be able to participate in the focus group.

Research data will be kept in cabinets that are locked except when in use, and access to data stored in computers will be password protected. The Yale University Human Investigation Committee and the National Institute of Child Health and Human Development (the sponsor of the study) may inspect study records. All published results will use group data. The audiotapes we produce from our discussions will be erased 12 months after the completion of the study and after the accuracy of their transcription has been confirmed.

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The focus groups will last approximately an hour and a half (with a 15 min break halfway through the meeting). Each participant will receive a $30 gift card for participating in the focus group.

Analyze focus group data and refine our conceptual model:
We will analyze the data using the principles of grounded theory, including the constant comparative method for systematic inductive analysis[92 93]. We will review a subset of transcripts to identify broad themes using open coding, analyzing data from each focus group to identify emerging concepts and use them as probes in the subsequent groups. To enhance inter-rater reliability, each of the team members will review and code the transcripts independently, and coding will be compared for agreement. We will use the ATLAS Ti software to electronically apply the manual codes to the textual data. Findings from these focus groups, with data from our PlayForward RCT, will be applied to refine a model of the dynamics of risk, decision-making, and positive health promotion in this new population with the new focus on HTC.

Modify intervention manuals ("Game PlayBooks"):
Based on a process we developed for the PlayForward videogame[13,] we will use our newly refined conceptual model and the data from the focus groups to inform a new set of intervention manuals ("Game PlayBooks"). These Game PlayBooks will be used as working documents between the research team members throughout this Phase I project and during the subsequent Phase II project. In these documents, the theory-based behavior change components are outlined alongside the game design elements. Our manuals from our previous intervention will be updated to include all components for our focus on HTC. From these manuals and subsequently produced storyboards, we will produce adapted components of the game to be piloted in Stage 2 of the study.

Potential game design of PlayForward (note: final game will emerge from iterative process described above, but the following game design strategies are provided as a potential scenario):
As outlined above, PlayForward was designed to provide at-risk young minority adolescents (aged 11-14 years) the opportunity to acquire and practice skills to reduce sexual risk behaviors with the goal of HIV prevention. Through a highly iterative process of qualitative formative work with our target audience[10,85-88], we developed a two-dimensional, role-playing videogame about how the choices one makes in life impact both short-term and long-term life goals. The game involves an interactive world in which the player, using an avatar they have created, "travels" through life, facing challenges and making decisions in the context of a series of 12 stories and narratives that bring different risks and benefits and 5 skill-based highly interactive mini-games. The following are potential modifications to enhance the original game and address adolescent HTC (though the final game will emerge from the iterative process described above).

Game Design Strategies Approach.
Inspired by and building upon our experience developing the groundbreaking PlayForward: Elm City Stories, we will adapt the current game to include new challenges and storylines specific to HTC in high school adolescents. Concepts that combat barriers to HIV testing and connect to services for adolescents will be taught in a compelling, interactive, narrative style, punctuated by mini-games that focus on skills that address behavioral risks associated with HIV infection.

Narrative. In the game's narrative, the player will first have the opportunity to experience HIV testing and counseling vicariously through role-play. The player will help another character in the story (who has been having unprotected sex) get tested. Later in the game, the player will be able to use the knowledge and skills gained from this experience to get tested his- or herself. Through the game's narrative, the player will have several opportunities to experience HIV testing and counseling, thus affecting his/her perceptions related to HIV testing and counseling and increasing their self-efficacy to get tested in real life.

Mini-Games. A number of mini-games that focus on increasing knowledge and behavioral skills related to HTC and HIV risk will also by included. For example, "Sexual Web" allows a player to explore how HIV and other

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STDs spread by playing different characters at different times in an evolving social setting. "Know Sense" gives players a chance to take on other characters' misconceptions about HIV testing and counseling and establish themselves as a thought leader on the subject. "Refusal Power" arms players with realistic refusal strategies for risky behavior. "Me Power" encourages a growth mindset and prepares players to take on "Priority Sense", where players must learn to balance long- and short-term goals.

Stage 2: Pilot test adapted PlayForward videogame (*PlayTest!)*
Design: We will enroll 30 adolescents that have not participated in the focus groups related to this project to test PlayForward using a pre/post design. During their initial visit with study staff, adolescents will answer demographic questions and questions on intentions to get HIV testing and counseling[95], HIV/AIDS Knowledge (HIV-KQ)[96], and other HIV education (including other education about or promotion of HTC) received. At the subsequent session, participants will then begin the gameplay portion of the project, where participants will play PlayForward on a tablet computer for 1 hour, two times per week for 3 weeks in a secured, private location (to accumulate 6 hours of gameplay). This total duration and number of sessions is consistent with those found in effective health promotion interventions among adolescents and with the amount of time adolescents play videogames[94]. After three weeks, gameplay ends and the participants will answer questions regarding intentions to get HIV testing and counseling[95], HIV/AIDS Knowledge (HIV-KQ)[96], and other HIV education (including other education about or promotion of HTC) received at this time point. Additionally, participants will be asked game play experience questions. The goal of the game-play experience questions are to learn whether adolescents thought playing the game was fun, boring, or interesting, and what they ~~you~~ would change about the game, the characters, and the storylines to make it better. Questions such as: What you thought the goal of the game was? Your favorite and least favorite moment in the game? Was the game fun? will be asked. After the participants answer their 3 week assessment questions, there is no interaction with the study staff again until the 6 week follow-up (i.e. there is down time between the 3 week and 6 week assessment; no gameplay occurs). Six weeks from the start of the study, participants will again be asked questions on intentions to get HIV testing and counseling[95], HIV/AIDS Knowledge (HIV-KQ)[96], and other HIV education (including other education about or promotion of HTC) received.

Measures: We will collect data on participant demographics at baseline. We will collect data on satisfaction with game play/acceptability and feasibility at the end of the 3 weeks of gameplay, and in-game data collected by the new PlayForward game software during gameplay sessions[89]. At baseline, 3, and 6 weeks, we will collect data on intentions to get HIV testing and counseling[95], HIV/AIDS Knowledge (HIV-KQ)[96], and other HIV education (including other education about or promotion of HTC) received. Participants will be provided compensation for completion of the baseline assessments ($30 gift card), and assessments at 3 and 6 weeks ($35 gift cards for each set of assessments). The total possible compensation for this stage of the study is $100 per participant.

Assessment Questions		Baseline	3-Weeks	6-Weeks
Demographics		X		
Intentions around HIV Testing/Counseling		X	X	X

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HIV/AIDS Knowledge		X	X	X
Other HIV/AIDS Education Assessment		X	X	X
Gameplay Experience			X	

Data analysis strategy: Baseline participant characteristics as well as assessment items (quantitative and qualitative) used to assess acceptability and feasibility of the intervention will be analyzed using descriptive statistics (quantitative data) and thematic coding (qualitative data). We will conduct a longitudinal analysis from baseline across 3- and 6-weeks to examine changes in i) intentions to seek HTC; ii) rates of HTC; and iii) knowledge about HIV/AIDS. In general, we will use two-tailed tests and p-values smaller than 0.05 will be considered to indicate statistical significance. When necessary, however, we will use appropriate adjustment of the level of significance (alpha) to account for multiple statistical tests. All of these analyses will be exploratory given the study sample size. Findings from these analyses in combination with the acceptability and feasibility assessments will be critical in informing the sample size needed to provide power to detect significant differences between the game and a control condition in a subsequent full-scale randomized trial to be conducted through a Phase II proposal. The product and data that result from Phase I will be used to prepare for Phase II.

Overview of study design for Phase II

Phase II will be conducted over the course of two years.

Stage 1: Videogame adaptation (Aim 1), establishment of web-based system and work with implementation and commercialization partners (Aim 2)

Conduct focus groups (4 focus groups of 5 adolescents each):

We will conduct focus groups according to standard procedures[99] and building on the formative work we have accomplished with the Phase I study. We anticipate that 4 focus groups will be adequate to achieve thematic saturation[100]. Examples of potential focus group questions are: "*What things worry you about getting tested for HIV?"* and *"What might help with this*?" and *"Who do kids turn to for advice or support?"* In addition to asking adolescents open-ended questions, we will use creative methods (e.g., art projects, photograph activities, and storytelling) to promote discussion with the adolescents. Participants will receive gift cards as compensation for engaging in the focus groups and refreshments and transportation will be provided as needed.

Analyze focus group data, refine our conceptual model, expand the intervention manuals ("Game PlayBooks") and produce new game content:

We will analyze the data using the principles of grounded theory, including the constant comparative method for systematic inductive analysis[101,102]. We will review a subset of transcripts to identify broad themes using open coding, analyzing data from each focus group to identify emerging concepts and use them as probes in the subsequent groups. To enhance inter-rater reliability, each of the team members will review and code the transcripts independently, and coding will be compared for agreement. We will use the ATLAS Ti software to electronically apply the manual codes to the textual data. Findings from these focus groups and data from the Phase I study will be applied to refine a model of the dynamics of risk, decision-making, and positive health promotion in this new population with the new focus on HTC. Based on a process we developed for the

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PlayForward videogame[12], we will use our newly refined conceptual model and the data from the focus groups to inform expanded intervention manuals ("Game PlayBooks"). These Game PlayBooks will be used as working documents between the research team members throughout the Phase II project. In these documents, the theory-based behavior change components are outlined alongside the game design elements. Our manuals from our previous intervention will be updated to include all components for our focus on HTC. From these manuals and subsequently developed storyboards, we will produce adapted and new components of the game to be built into the web-based system and tested in Stage 2 of the study. Going into Stage 2 of Phase II for this protocol, we will also work with partners to further execute strategies for widespread distribution of the adapted game.

Conduct individual interviews with stakeholders (n=15): To further assist with creating new storylines and content for the web-based version of the game, we will conduct qualitative semi-structured one-on-one interviews with key stake-holders (i.e. school administrators, counselors, teachers, nurses, site coordinators, and community partners).

Stage 2: Randomized controlled trial of the *PlayTest!* videogame (Aim 3)

Design: We will enroll 296 girls and boys who attend one of our partner programs. Eligible individuals will be assigned to either the ***PlayTest!*** arm (n=148) or a set of attention/time control games (n=148). All participants will play one to two sessions per week for four weeks for a goal of 5 hours of gameplay, which will take place through the web-based game. All gameplay will occur on site at their programs. This total duration and number of sessions is consistent with those found in effective HIV prevention interventions, with the amount of time adolescents play games[36], and the amount of gameplay observed among participants in the ***PlayForward*** study[97]. We will collect follow-up data on all participants at four weeks (immediately following completion of gameplay), three and six months.

Adequacy of sample size: A sample size calculation was done using the G*Power software. An effect size of 0.27, was estimated (conservatively) based on previous research [103]. With equal numbers of subjects in each group, and alpha = 0.05, to provide 85% power to detect a difference in HTC rates at six months controlling for history of testing, sex, and ethnicity, a sample of 118 per group (total N = 236) is required. Based on adherence rates from our test of the original ***PlayForward*** game we assume 80% retention at 6 months. To account for the 20% dropout we will seek to enroll 296 participants.

Randomization: We will use a stratified randomization procedure[104] to assign participants to one of the study arms. Gender, race/ethnicity, and age will be included in the randomization algorithm because these variables have been found to be important predictors of HTC in adolescents[103]. The stratification would be as follows two gender groups (girl vs. boy) , two ethnic groups (Hispanic vs. non-Hispanic) , three groups for race (White, African-American, Other) and two groups for age – (14, 15, 16 vs. 17 and 18). A block size of 6 will be used for the stratification process.

Treatment conditions: The research staff will orient the participants to the use of either ***PlayTest!*** or the control videogames. Players in both groups will play through an online tutorial demonstrating the mechanics of the game. Each player will use a dedicated device to access their game on the web and a set of headphones that they will use during each gameplay session. The research staff will oversee all gameplay to ensure that participants are playing and to field any questions. The control videogames (**see below**) will be engaging and fun but will be devoid of relevant content.

Assessments: We will assess participant characteristics (demographic), outcomes, and process measures (Table 1). For outcomes, we will collect data on actual HTC and assess a variety of mediators and moderators among teens (e.g., attitudes, intentions, knowledge). To measure actual testing in our participants, we will work with health care professionals at school clinics located on the premises of our partner sites to determine if students who participated in our study subsequently got tested. This data will be collected based on the protocol of the specific clinic, and the participants' personal health information will be de-identified (including results) before being

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given to research staff. We will conduct follow-up assessments at four weeks (immediately after conclusion of gameplay), three and six months. Participants will receive gift cards as compensation for completion of assessments at each of the time points. For process measures, we will conduct qualitative interviews with each of the participants who played ***PlayTest!,*** as we have done previously[105]. We will collect gameplay experience satisfaction/feasibility/acceptability[105] data and abundant data on the gameplay process is collected through the software[98] (including overall time spent playing the game and specific components of the game and performance in each component).

Table 1. Schedule of Assessments

Assessment	Baseline	Week 4	Month 3	Month 6
Participant history and demographic data: 10 items on the individual (i.e. gender, age, education, HTC history)[8].	**X**			
School-based health centers	**X**	**X**	**X**	**X**
Information About HIV Testing	**X**	**X**	**X**	**X**
Behaviors—Youth Risk Behavior Survey (YRBS) (includes questions on sexual activity and HIV testing)[3]	**X**	**X**	**X**	**X**
Knowledge/Information[107] including knowledge about STIs and HIV and HTC	**X**	**X**	**X**	**X**
Beliefs About STIs and HIV	**X**	**X**	**X**	**X**
Attitudes About HIV	**X**	**X**	**X**	**X**

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Attitudes about STI and HIV Testing	**X**	**X**	**X**	**X**
Intentions Around STIs and HIV Testing	**X**	**X**	**X**	**X**
Self-Efficacy Around STI and HIV Testing	**X**	**X**	**X**	**X**
Self-Efficacy about Overall Health	**X**	**X**	**X**	**X**
Education Around STIs and HIV	**X**	**X**	**X**	**X**
Gameplay satisfaction/acceptability/feasibility, time played for each session and overall time played: 12-item Likert scale[105]		**X**		
In-game data collected by adapted ***PlayTest!*** software (intervention group only)[98].		**X**		

Data collection and management: All data collected from the assessments will be entered directly into the secure web-based system, Qualtrics. Qualtrics is a Yale University supported system that collects and analyzes survey data. Data will be entered into the Qualtrics system by the participant themselves via an iPad or their cell phone. Additionally, the web-based Oncore database will be used to store participant contact information and assist with managing follow-up assessment dates. A copy of assessment data will be pulled from Qualtrics for each participant and attached to the participant's file in Oncore. This method limits data entry-associated errors. Before enrolling participants into the intervention, we will conduct a pilot test with two to three participants to assess acceptability and usability of the game, make changes as needed, and confirm data collection procedures.

Furthermore, to collect data on the study's primary outcome of increasing HIV testing and counseling in this age group, we will work with the school based health centers at our partner sites. The research staff will:

- Provide the SBHC facilitator (i.e., office manager, APRN) with a hard copy of the *Student Identification Form* that includes the names of all students who have enrolled in the study. The *Student Identification Form* will also include the study numbers for all students (see below).

Student Identification Form

Participant Name:	Participant Study ID:

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- Provide the SBHC facilitator with a separate password protected excel form that is on a flash drive (*Health Center Participation Form*). *The Health Center Participation Form* will include study numbers for the students who are enrolled in the project and allows the SBHC facilitator to track students who utilized the SBHC over the duration of the project (see form below).

Health Center Participation Form

Participant Study ID:	STI Test? (Y or N)	If Yes, STI Test Date	HIV Test? (Y or N)	If Yes, HIV Test Date

- Both the hard copy of *the Student Identification Form* and the flash drive that houses the *Health Center Participation Form* will be kept in secure separate locations in the school based health clinic (two lockboxes that will be provided by the play2PREVENT Team)

The SBHC facilitator will:

- Enroll each student with a completed enrollment form into the school based health center database.
- At the end of each month, the facilitator will check the *Student Identification Form* to identify any students that have utilized the school based health center during that month.
    - If a student has used the health center, then the facilitator will record pertinent information on the *Health Center Participation Form* that is on the password protected excel document for the monthly time period in review.
- At the end of each month, the facilitator will meet with a member of the play2PREVENT team for approximately 10-15 minutes. During this brief meeting the SBHC facilitator and the play2PREVENT team member will print the *Health Center Participation Form* for the time period at hand and both parties will sign-off on its completeness. The printed sheet will then be placed in the secured lockbox with the USB drive.
- Use the 3000z billing code for participants that come in for a STI/HIV test to protect privacy during insurance billing.

Data analysis

Phase 2: Data analyses general considerations: All statistical analyses will be conducted based on the "intent-to-treat" principle, through the use of either SPSS or SAS statistical packages.

Statistical analyses: **Primary outcome:** The primary outcome will be the proportion of participants who engage in HTC within the six-month study period. Rates of HTC among intervention and control participants at six months will be compared using Fisher's exact test and a 2-sided test at the 0.05 level. **Secondary outcomes:** To address the secondary outcomes we will use repeated measures ANCOVAs (with Bonferroni corrections to account for multiple statistical tests). The models will include attitudes, perceived barriers, perceived norms, intentions, self-efficacy, and knowledge as dependent variables, with study condition as the independent variable, and sex, ethnicity, and history of testing as covariates. **Mediators and moderators:** Data will be collected on potential mediators and moderators and examined using conventional methods[113]. Baseline levels of these mediators and moderators will be used in the models to assess whether these variables affect the primary or secondary outcomes. In addition, because these variables might change over time during participation in the study, they will also be considered as time-varying covariates. **Mediators:** Based on our logic model[12] that will guide the development of the proposed intervention, we predict that 1) attitudes, 2) perceived barriers, 3)

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perceived norms, 4) intentions, 5) self-efficacy, and 6) knowledge will mediate the effects of the intervention on HTC at 6 months. The selection of mediators is based upon the logic model and given the proposed game will have many different components (as our current ***PlayForward*** game does), and given our experience of including all of these components into a game intervention, this selection of mediators was carefully guided by the process of constructing the logic model. We will use the criteria proposed by Baron and Kenny ~~(1986)~~[113] to test the relationships among the outcomes and presumed mediators. According to these criteria, four conditions should be met to establish mediation. We outline these conditions using our specific hypothesis that intentions mediate the relationship between the study condition (intervention or control) and HTC as an example. The first condition is that the study condition is directly related to HTC. Second, the intervention condition has a direct effect on the mediator (intentions). Third, intentions have a direct effect on HTC, when the study condition is controlled. Fourth, if intentions mediate the intervention condition-HTC relationship, the direct effect of the study condition on HTC is reduced or eliminated after controlling for intentions. To test the significance of mediation effect, which is called indirect effect, we will calculate Sobel's test[114-116] for each proposed mediator. Sobel's test determines the significance of the mediation effect by testing the null hypothesis that the indirect effect coefficient is zero (i.e. whether the indirect effect of the independent variable on the dependent variables is significantly different from zero). **Moderators**: Variables that predict the outcome variable (first substance use) differently between treatments will be considered to be moderators using the model outlined by Kraemer et al[117]. In order to be considered a moderator, the variable must be present prior to randomization and must not be related to the independent variable (***PlayTest!*** *vs.* control games). Pre-randomization variables that interact with the independent variable in predicting the outcome variable (HTC) will be considered moderators of treatment. Variables that predict the outcome variable but do not significantly interact with treatment condition will be classified as nonspecific pre-randomization predictors.

Collection and analysis of the in-game data: We will build on systems we have developed to analyze the data collected by the game software or the in-game data[98], which will serve as the foundation for analytics system built into the game. Briefly, using Player Game State Data (the traditional save/load data so a player can save their progress and pick up later where they left off) and Activity Logging Data (the relevant time-stamped player actions during gameplay), we will examine the paths taken and decisions made by each player, documenting their exposure to content and the "learning curve" from the in-game data.

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*

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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.

Phase I:4 focus groups of 5 adolescents each (n = 20), boys and girls, aged 15-18 will participate in the focus groups and 30 adolescents, boys and girls, aged 15-18 will participate in the pilot testing of the adapted game. These adolescents will be recruited from the school-based or after-school programs, or community youth programs that we already have established partnerships with, such as LEAP, Hamden Youth Center, and the local public library.

Phase II: Recruitment/enrollment for this portion of the project (including focus groups and the RCT) will take place at one of the community high school programs, youth programs, or local health programs with which we already have partnerships (see Letters of Support). Our team has a successful track record of establishing a consistent presence at our partner sites and now has close working relationships with the program staff that are fully engaged in the recruitment process. Sites for recruitment and participation include but are not limited to: Wilbur Cross High School, the Leadership, Education, & Athletics in Partnership (LEAP) Program, Hillhouse High School and Planned Parenthood of Southern New England (PPSNE).

7. 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.

☒Children	☒ 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 ☒

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

For **Phase I**: Participants must: 1) be 15-18 years of age. For the pilot-testing phases, participants must also be able to participate in a mobile videogame (willing to sit with a tablet computer for 60 minutes/session to play the game). Eligibility will be determined by the research team.

For **Phase II**: Participants must: 1) be 14-18 years; For Stage 2 of this phase, participants must also: 1) be able to participate in a web-based videogame (willing to sit for 60 minutes/session to play the game); 2) not have been tested for HIV in the past year; 3) be able to provide assent/parental/guardian consent; and 4) have a completed and signed enrollment form for their school's health clinic allowing them, if they choose, to access the clinic for testing and health care.

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

Eligibility will be determined by the research team including Ms. Pendergrass, Dr. Hieftje, and the Research Assistants (TBD). The research assistant/ research team will 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. 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 will focus on promoting healthy behaviors and on providing strategies to assist adolescents in making decisions about the many challenges they face including the risk for HIV. If an individual or their parent/guardian indicates that they do not wish to participate, there will be no further involvement in the study.

10. **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. 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 P.I. and other relevant research staff will have access to the data.

Playing *PlayTest!* pose a potential psychological risk in that we address sensitive issues around sex, HIV testing and counseling, and its consequences. Research staff will be available to provide assistance to the 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 risky behaviors. Again, the Research staff will available to assist the participants, the program sites staff, and the research staff members administering the assessments if there appears to be any distress around the questions being asked. If participants need additional or more intensive attention, Dr. Fiellin will provide consultation to the participant.

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

A number of precautions will be actively integrated into the research procedures to protect the confidentiality and anonymity of all participants. All research staff and the staff and volunteers participating in the intervention 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 P.I.'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 guardian/parent 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 guardian/parent 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.

In the unlikely event that a participant involved with the study experiences a serious medical or psychological complication, that requires further attention, this would be reported to Dr. Fiellin who will then determine if further consultation is required without divulging the name of the individual, if this appeared appropriate and necessary. Dr. Fiellin would then be responsible for ensuring that the needs of the individual were addressed.

12. **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.)

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a. What is the investigator's assessment of the overall risk level for subjects participating in this study? *Minimal risk for those participating in this study*

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 for those participating in this study*

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

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews quarterly. During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator or the Human Investigative Committee (HIC) have the authority to stop or suspend the study or require modifications.
This protocol presents minimal risks to the subjects 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 any appropriate funding and regulatory agencies. The investigator 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 principal investigator. 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. Data and safety monitoring procedures in this study include collection and monitoring of paper-based questionnaires and an organizational structure of clearly defined tasks assigned to all research personnel involved in the conduct of this study. We will keep a thorough record of research activities and completion of scheduled assessments.

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*

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

Phase I Data analysis strategy: Baseline participant characteristics as well as assessment items (quantitative and qualitative) used to assess acceptability and feasibility of the intervention will be analyzed using descriptive statistics (quantitative data) and thematic coding (qualitative data). We will conduct a longitudinal analysis from baseline across 3- and 6-weeks to examine changes in i) intentions to seek HTC; ii) rates of HTC; and iii) knowledge about HIV/AIDS. In general, we will use two-tailed tests and p-values smaller than 0.05 will be considered to indicate statistical significance. When necessary, however, we will use appropriate adjustment of

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the level of significance (alpha) to account for multiple statistical tests. All of these analyses will be exploratory given the study sample size. Findings from these analyses in combination with the acceptability and feasibility assessments will be critical in informing the sample size needed to provide power to detect significant differences between the game and a control condition in a subsequent full-scale randomized trial to be conducted through a Phase II proposal. The product and data that result from this Phase I project will be used to prepare a Phase II STTR application.

Phase II Data analysis strategy: All statistical analyses will be conducted based on the "intent-to-treat" principle, through the use of either SPSS or SAS statistical packages.
Statistical analyses: **Primary outcome:** Due to COVID-19's impact on this study's initial primary outcome of the number of participants that were tested for HIV at the 6 month timepoint, the primary outcome has been modified. Behavioral outcomes are influenced by attitudes and intentions; therefore, we will explore attitudes and intentions in our study, with **attitudes about around HTC** as the new primary outcome. After a thorough review of existing literature, the team decided that the primary outcome would be changed to measuring participant's attitudes around HTC at 6 months for the full cohort, with intentions and behaviors being assessed as secondary outcomes. **Secondary outcomes:** To address the secondary outcomes we will use repeated measures ANCOVAs (with Bonferroni corrections to account for multiple statistical tests). The models will include attitudes, perceived barriers, perceived norms, intentions, self-efficacy, and knowledge as dependent variables, with study condition as the independent variable, and sex, ethnicity, and history of testing as covariates. **Mediators and moderators:** Data will be collected on potential mediators and moderators and examined using conventional methods[113]. Baseline levels of these mediators and moderators will be used in the models to assess whether these variables affect the primary or secondary outcomes. In addition, because these variables might change over time during participation in the study, they will also be considered as time-varying covariates. **Mediators:** Based on our logic model[12] that will guide the development of the proposed intervention, we predict that 1) attitudes, 2) perceived barriers, 3) perceived norms, 4) intentions, 5) self-efficacy, and 6) knowledge will mediate the effects of the intervention on HTC at 6 months. The selection of mediators is based upon the logic model and given the proposed game will have many different components (as our current ***PlayForward*** game does), and given our experience of including all of these components into a game intervention, this selection of mediators was carefully guided by the process of constructing the logic model. We will use the criteria proposed by Baron and Kenny ~~(1986)~~[113] to test the relationships among the outcomes and presumed mediators. According to these criteria, four conditions should be met to establish mediation. We outline these conditions using our specific hypothesis that intentions mediate the relationship between the study condition (intervention or control) and HTC as an example. The first condition is that the study condition is directly related to HTC. Second, the intervention condition has a direct effect on the mediator (intentions). Third, intentions have a direct effect on HTC, when the study condition is controlled. Fourth, if intentions mediate the intervention condition-HTC relationship, the direct effect of the study condition on HTC is reduced or eliminated after controlling for intentions. To test the significance of mediation effect, which is called indirect effect, we will calculate Sobel's test[114-116] for each proposed mediator. Sobel's test determines the significance of the mediation effect by testing the null hypothesis that the indirect effect coefficient is zero (i.e. whether the indirect effect of the independent variable on the dependent variables is significantly different from zero). **Moderators**: Variables that predict the outcome variable (first substance use) differently between treatments will be considered to be moderators using the model outlined by Kraemer et al[117]. In order to be considered a moderator, the variable must be present prior to randomization and must not be related to the independent variable (***PlayTest!*** *vs.* control games). Pre-randomization variables that interact with the independent variable in predicting the outcome variable (HTC) will be considered moderators of treatment. Variables that predict the outcome variable but do not significantly interact with treatment condition will be classified as nonspecific pre-randomization predictors.

Collection and analysis of the in-game data: We will build on systems we have developed to analyze the data collected by the game software or the in-game data[98], which will serve as the foundation for analytics system built into the game. Briefly, using Player Game State Data (the traditional save/load data so a player can save their progress and pick up later where they left off) and Activity Logging Data (the relevant time-stamped player

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actions during gameplay), we will examine the paths taken and decisions made by each player, documenting their exposure to content and the "learning curve" from the in-game data.

All data collected from the assessments will be entered directly into the secure web-based system, OnCore, Yale's enterprise-wide clinical research management system. OnCore is a fully integrated system development by Forte, which includes three modules: 1) Clinical research management (CRM); 2) Bio-specimen management (BSM); and 3) Patient registry. This project will utilize the CRM module as the electronic data capture system for all case report form data and to support subject tracking. Data will be entered into the OnCore system either by research staff, or with the more sensitive assessments, by the participant themselves. This method limits data entry-associated errors. Before enrolling participants into the intervention, we will conduct a pilot test with two to three participants to assess acceptability and usability of the game, make changes as needed, and confirm data collection procedures.

New proposed plan for analysis approach due to COVID-19

1. Revise power calculations to ensure that a clinically meaningful effect size for the new primary outcome (attitudes around HTC at 6 months in the full cohort) can be detected.
2. Examine **attitudes** around HTC as primary outcome at 6 months in the full cohort.
3. Examine **intentions** to get tested at 6 months in full cohort.
4. Examine **HTC** at 6 months in smaller cohort of students that were able to reach the full 6 months of the study without being impacted by the pandemic (N=135). This study is not powered to detect a difference at this smaller sample size.
5. Examine **HTC** at 3 months for a sub-cohort of students who were able to reach that time point without being affected by the pandemic (N=237; the study is powered for this outcome at n=236, but at 6 months). While we technically would be powered at this time-point, we would have cut our time to reach the outcome in half, posing a considerable limitation.
6. Examine attitudes and intentions at 3 months (N=237) (to be used in conjunction w #4 directly above).

New data analysis plan suggestion from study's Data Safety Monitoring Board member

- Use mixed models for the repeated measures analyses of the dimensional outcomes, as they use all available data on an individual and are generally robust to data missing at random. The repeated measures ANOVA approach that is mentioned in the document is meant for complete data and is not flexible in accounting for the correlations within individual.

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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/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

B. DRUGS/BIOLOGICS ☒N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☐
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☐
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☐
4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☐
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☐

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Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.
Write here

3. **Source:** Identify the source of the drug or biologic to be used. *Write here*

a) Is the drug provided free of charge to subjects? ☐YES ☐NO
If yes, by whom? *Write here*

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
Write here

Check applicable Investigational Drug Service utilized:

☐ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

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5. Use of Placebo: ☒Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. *Write here*

b) State the maximum total length of time a participant may receive placebo while on the study.
Write here
c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
Write here
d) Describe the procedures that are in place to safeguard participants receiving placebo.
Write here

6. Continuation of Drug Therapy After Study Closure ☒Not applicable to this project
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☐ NO If no, explain why this is acceptable. *Write here*

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☐No

If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request; AND

Your request must be reviewed and approved in writing by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. Background Information: Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
Write here
3. Source:
a) Identify the source of the device to be used. *Write here*
b) Is the device provided free of charge to subjects? ☐Yes ☐No

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4. **Investigational device accountability**: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*

   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. Targeted for enrollment at Yale for this protocol: Phase I: 50; Phase II:316
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: *Write here*

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☒ Posters	☒ Mass email solicitation to school parents	☐ Telephone
☒ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☒ Other: Sign-ups through after-school and school based partners, announcements in health classes, lunch-wave recruitment, open houses & report card nights at the schools, school-wide announcement		

* 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. (See below)
b. Describe how potential subjects are contacted. (See below)
c. Who is recruiting potential subjects? (See below)

Participation in this study will be strictly voluntary, confidential and non-discriminatory. Participants will be enrolled while they are on-site at one of the participating programs. The study will be advertised in myriad ways including: posters, flyers, letters, sign-ups through afterschool programs, open houses, announcements and

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informational table set up during lunch waves, open houses and report card nights. Announcements will also be made during health classes, and mass emails will be sent out to parents/guardians. Participants 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. If a participant or their guardian/parent indicates that they do not wish to participate, there will be no further involvement in the study. We will also obtain agreement from the appropriate administrator at the participating program. The research staff will be recruiting potential subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
   Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
   ☐Yes, all subjects
   ☐Yes, some of the subjects
   ☒No

   If yes, describe the nature of this relationship. *Write here*
5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
   Choose one:
   ☐ For entire study
   ☐ For recruitment/screening purposes only
   ☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

   i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: *Write here*

   ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

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Participation in this study will be strictly voluntary, confidential and non-discriminatory. Participants will be enrolled while they are on-site at one of the participating programs. Potential participants will meet with the Research Assistant to discuss participation in the study. If the participant is interested, the Research Assistant will discuss the study with their guardian/parent. We will provide the adolescents and their parents 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.

In Phase I we will employ waived consent. Parents who do not wish for their children to participate will contact the project director.

In Phase II we will obtain informed written assent from the participant and written informed consent from their guardian/parent. For interested participants, study enrollment packets will be sent home that include: a study eligibility checklist, an infographic of the study, a parental consent document, and a school-based health center enrollment form (see attached documents). Research staff will work with school personnel to collect completed enrollment packets that consist of a completed and signed parental consent form and a completed and signed school-based health center enrollment form. After the completed study enrollment packet has been received by the study team from the school personnel, the research assistant will check the forms for completeness and the Research Coordinator will subsequently verify their completeness. The Research Coordinator will then turn the completed school-based health center enrollment forms into the school-based health center staff, and keep the school-based health center enrollment verification documents for our records along with the signed parental consent form.

During the first meeting with participants once the study begins, the participants will again be provided with an age-appropriate description of the study and told about what they might expect for the duration of the study. If the participant is still interested, they will then sign an adolescent assent form.

For both phases, if a participant or their guardian/parent indicates that they do not wish to participate, there will be no further involvement in the study. We will also obtain agreement from the appropriate administrator at the participating program.

Additionally, we may ask participants' parents to sign a form (Parent Permission to Photograph) to allow our research staff to take photographs of their teen during game play sessions. Photographs may be used for purposes of the study, including posting them on our websites, play2PREVENT.org, foragirl.com and our social media. Parents do not have to give permission for their teen's photograph to be used and may request that the pictures be removed at any time if they do agree. Parents will also be informed that not agreeing to allow their teen to be photographed does not affect their teen's participation in the study.

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. For focus groups, we will employ waived consent. Parents who do not wish for their children to participate will contact the project director. For pilot-testing and the Randomized

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Controlled Trial, we will obtain informed written assent from the participant and written informed consent from their guardian/parent.

8. Non-English Speaking Subjects: 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 speakers will not be able to participate in the research project. However, parental information sheets and consent forms will be translated into Spanish for parents of adolescents.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only) For Phase I and Focus Groups in Phase II*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☒ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☒ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☐ Requesting a waiver of consent:

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

☐ Entire Study

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

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Names, telephone phone numbers, addresses, email addresses, parent/guardian names, parent/guardian phone numbers, and parent email addresses will all be collected.

2. How will the research data be collected, recorded and stored?

Data collection and management: All data collected from the study assessment questions will be entered directly into the secure web-based system, Qualtrics. Qualtrics is a Yale University supported system that collects and analyzes survey data. Participants will complete their study assessment questions via a link on their individual iPads or cellphones. Their answers will automatically be uploaded from the portable device onto the Qualtrics system.

Additionally, the web-based Oncore database will be used to store participant contact information, randomize participants, and assist with managing follow-up assessment dates. A copy of assessment data will be pulled from Qualtrics for each participant and attached to the participant's file in Oncore. This method limits data entry-associated errors.

The first set of assessments will be conducted at baseline and will collect the most data; subsequent assessments will be conducted at follow-up intervals. Each assessment will require approximately 30 minutes of the participant's time. In addition, data for this study is collected via the videogame software during the participant's game play and will be stored in a secure database.

Furthermore, to collect data on the study's primary outcome of increasing HIV testing and counseling in this age group, school-based health center staff will utilize a password protected Excel form that is on a flash drive to track students who utilized the SBHC over the duration of the project. This password protected flash drive will be kept in a secure locked cabinet in the school-based health center.

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3. How will the digital data be stored? ☐CD ☐DVD ☒Flash Drive ☐Portable Hard Drive ☒Secured Server ☒Laptop Computer ☒Desktop Computer ☐Other
4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
   Confidentiality will be protected by having records identified by code number only with the master list including names kept in a sealed envelope in a locked file in the Principal Investigator's office. Data collection and storage will be conducted according to standardized protocols. All information will be identified by code and not linked to subject name except as described above. All data analyses will be performed under approved HIC protocols.

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

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.

1.

2. If appropriate, has a Certificate of Confidentiality been obtained? *Write here*

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(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 HIV testing and counseling. It is hypothesized that the participants enrolled in the pilot testing of the adapted PlayForward game will have lower rates of initiation of tobacco use at the follow-up periods. This research has the potential to benefit a large number of kids around the country and worldwide, because if in the pilot test the intervention is shown to be effective, then this program 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.

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Phase I: Each participant will receive a $30 gift card for participating in the focus group.
Participants will be provided compensation for completion of the baseline assessments ($30 gift card), and assessments at 3 and 6 weeks ($35 gift cards for each set of assessments). The total possible compensation for this stage of the study is $100 per participant.

Phase II: Each participant will receive a $25 gift card for participating in the focus group. For those participants in the randomized controlled trial, participants will be provided compensation for completion of the baseline assessments ($35 gift card), and assessments at 4 weeks ($20 gift card), 3 months ($20 gift card) and 6 months ($35 gift card). The total possible compensation for this stage of the study is $110 per participant.

Stakeholders who participate in the one-on-one interviews will receive a $20 gift card.

Key staff members at each school based health center at each of our partner sites will potentially receive a stipend for in school assistance with this study.

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 subjects will be incurred.
4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

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

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IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No ☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☒

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 ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

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

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

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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