HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: A Virtual Reality Videogame for E-cigarette Prevention in Teens

Principal Investigator: Kimberly Hieftje, PhD

Version Date: January 27, 2020

(*If applicable*) Clinicaltrials.gov Registration #: **NCT04054765**

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. Read the following instructions before proceeding: 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

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

The specific aims of Sub-study #1 are:

Specific Aim #1: DEVELOPMENT: We will update our current Invite Only VR prototype into a polished videogame intervention using input from 4 focus groups of 5 adolescents each (n = 20), aged 12-17 and the extant literature. These focus groups will inform the development of the VR videogame intervention, ***Invite Only VR***, for e-cigarette prevention among teens.

Specific Aim #2: EVALUATION: Conduct a pilot randomized controlled trial with 300 teens ages 11-15 comparing the Invite Only VR intervention vs. an attention/control non-health-related VR videogame, collecting assessment data at baseline, post-gameplay, three months and six months to determine:

a. the preliminary impact of the intervention on knowledge, intentions, perceptions, attitudes, social norms, self-efficacy and behaviors related to: i) initiation of e-cigarette use, ii) e-cigarette use cessation.
b. the intervention's acceptability and feasibility by collecting quantitative and qualitative data on teens' satisfaction and gameplay experience of the intervention.
c. preliminary evidence of the impact of ***Invite Only VR*** on players' perception and experience of social pressure and social norm development.

The specific aim for Sub-study #2 is

Specific Aim #1: EVALUATION: Conduct a quasi-experimental effectiveness trial of the Invite Only VR intervention using a pre-post study design with 400 teens ages 11-15, collecting assessment data at baseline and post-gameplay to determine:

a. the preliminary impact of the intervention on knowledge, intentions, perceptions, attitudes, social norms, self-efficacy and behaviors related to: i) initiation of e-cigarette use, ii) e-cigarette use cessation.
b. the intervention's acceptability and feasibility by collecting quantitative on teens' satisfaction and gameplay experience of the intervention.

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

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.

Tobacco use, including the use of e-cigarettes, is the leading cause of preventable disease and death in the United States[1] and is linked to cancer and cardiovascular diseases.[2] In 2016, 3.9 million middle/high school students used at least one tobacco product in the past 30 days and approximately 45% of middle/high school students used two or more tobacco products in the past 30 days.[1] Of particular interest, e-cigarettes have emerged as an introductory tobacco product among youth[3] due, in part, to their appealing flavors[4-6] and perception that they are safer than other products.[7-9] Given more than 80% of adult smokers begin using tobacco products such as e-cigarettes before the age of 18,[1] there is a

need to develop interventions that will help prevent e-cigarette experimentation among young adolescents; a population inherently vulnerable to tobacco initiation and the development of life-long tobacco use.

The use of virtual reality (VR) has emerged as an effective intervention approach to addressing a range of health issues, including phobias, social anxiety, post-traumatic stress disorder and pain management. Currently, no research exists on the efficacy of evidence-based VR videogames related to tobacco use prevention.

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.

The goal of this research study is to conduct a randomized controlled trial of the VR-based e-cigarette prevention intervention, ***Invite Only VR***, with the aim to prevent the initiation of e-cigarette use in teens by increasing their knowledge, decreasing their intentions to use e-cigarettes, influencing their harm perceptions and attitudes associated with e-cigarettes, and increasing behavioral skills associated with refusing peers involving e-cigarettes. ***Invite Only VR*** is an innovative, immersive intervention that may hold the promise to reducing e-cigarette initiation in teens.

For Sub-study #1:

We will conduct the proposed research for the study in two phases. Phase I consists of: (a) the continued development of our current ***Invite Only VR*** prototype into a polished videogame intervention using input from 4 focus groups of 5 adolescents each (n = 20), aged 12-17 and the extant literature. These focus groups will inform the development of the VR videogame intervention, ***Invite Only VR***, for e-cigarette prevention among teens (Specific Aim #1). In Phase II, we will conduct a randomized controlled trial with 300 teens ages 11-15 comparing the ***Invite Only VR*** intervention vs. an attention/control non-health-related VR videogame, collecting assessment data at baseline, post-gameplay, three months and six months to determine: 1) the preliminary impact of the intervention on knowledge, intentions, perceptions, attitudes, social norms, self-efficacy and behaviors related to initiation of e-cigarette use and e-cigarette use cessation, 2) the intervention's acceptability and feasibility by collecting quantitative and qualitative data on teens' satisfaction and gameplay experience of the intervention, and 3)preliminary evidence of the impact of ***Invite Only VR*** on players' perception and experience of social pressure and social norm development.

Conduct focus groups to gather data to inform refinement of the current videogame prototype, *Invite Only VR*.
We will conduct 4 focus groups (5 adolescents each) to collect feedback on the game content, art, narrative, and characters, and gameplay mechanics. We will use visual tools (e.g., storyboards, pictures) to facilitate the discussions. We will conduct the focus groups according to standard dual-facilitator procedures[11]. We anticipate that 4 focus groups will be adequate to achieve thematic saturation[12]. The focus groups will be conducted such that ideas and themes from one discussion inform discussion topics and prompts used in the next focus group. Participants will be compensated with a gift card for $25. Audio recordings of each session will be transcribed, reviewed and discussed by the research team to refine the videogame intervention. As a part of the game development, with parental permission we will invite selected students to the Yale recording studio on campus to provide voices for the videogame characters.

Conduct randomized controlled trial: We will enroll 300 adolescents to test ***Invite Only VR*** using a pre/post design to evaluate the preliminary efficacy of the videogame prototype, ***Invite Only VR***. Participants will be randomly assigned to play either Invite Only VR (n=115), or receive standard care as usual (n=115). Participants will accumulate between 1.5-2 hours of game play over 2 sessions (approximately one week, meeting twice). Participants will play the ***Invite Only VR*** game on a VR headset for 45 mins to 1 hour, one to two times per week for 2 weeks (to accumulate up to 1.5 - 2 hours of gameplay). This total duration and number of sessions is consistent with those found in effective smoking prevention interventions among adolescents and with the amount of time adolescents play videogames[13]. Participants will have a 10 min break in the middle of each session and will be instructed that they may take additional breaks as needed.

Measures. We will collect data on participant demographics at baseline. At baseline and immediately after gameplay, and again at 3 and 6 months post gameplay, we will collect data on intentions to initiate smoking[14], self-efficacy for refusing offers of e-cigarettes and other tobacco products[15], perceived social norms related to smoking[16], attitudes about smoking[17], and smoking behavior[18] using validated questionnaires. Finally, we will assess satisfaction with game play and acceptability and feasibility of the intervention by collecting self-report data at the end of the game play period. All assessments will be conducted via face-to-face interviews with a research assistant and each adolescent.

Study locations. For the focus groups and pilot-testing, the study will take place at one of the after-school programs with which the play2PREVENT Lab has ongoing partnerships including but not limited to: Wilbur Cross High School (which serves 1300 students from 9th to 12th grade), Hamden Youth Center (which serves roughly 75 adolescents in the 6th through 12th grade, and the Milford Middle School District (which serves 1300 students the majority of whom are between the ages of 11 and 14), and LEAP (which serves over 1000 children between the ages of 7-18). For the randomized controlled trial, we will enroll students from the Milford Middle School District between the ages of 11-15.

Participants, screening, and consent. In collaboration with community program staff, we will discuss the study with interested parents and adolescents and collect eligibility screening data. If the participant is eligible and interested we will proceed with the consent procedures that will differ by phase of the research. For focus groups, we will give information sheets to the adolescents and to their parents describing the purpose of and protocol for the focus groups. Parents who do not wish for their children to participate will contact the project director. No forms will be signed for focus groups. For the randomized controlled trial, we will obtain written, informed assent (adolescent) and consent (parent).

In addition to paper forms for parental consent for participation in the randomized controlled study, we will also provide a web-based form for parents to review and electronically sign through Yale Qualtrics.

For Sub-study #2:

We will conduct a quasi-experimental study with 400 teens from the Seattle School District ages 11-15 of the ***Invite Only VR*** intervention collecting assessment data at baseline and post-gameplay to determine: 1) the preliminary impact of the intervention on knowledge, intentions, perceptions, attitudes, social norms, self-efficacy and behaviors related to initiation of e-cigarette use and e-cigarette use cessation, and 2) the intervention's acceptability and feasibility by collecting quantitative on teens' satisfaction and gameplay experience of the intervention.

Quasi-experimental study design: With the assistance of our program partners at Seattle Schools, we will enroll 400 adolescents to test ***Invite Only VR*** using a pre/post design to evaluate the preliminary efficacy of the videogame prototype. All participants will play Invite Only VR. Participants will accumulate between 1.5-2 hours of game play during their class or program time. Participants will play the ***Invite Only VR*** game on a VR headset for 45 mins to 1 hour, one to two times (to accumulate up to 1.5 - 2 hours of gameplay) during their advisory/common time in school (non-class time). This total duration and number of sessions is consistent with those found in effective smoking prevention interventions among adolescents and with the amount of time adolescents play videogames[13]. Program partners will be instructed to give participants a 10 min break in the middle of each session and will be instructed that they may take additional breaks as needed.

Measures. We will collect data on participant demographics at baseline. At baseline and immediately after gameplay, we will collect data on intentions to initiate smoking[14], self-efficacy for refusing offers of e-cigarettes and other tobacco products[15], perceived social norms related to smoking[16], attitudes about smoking[17], and smoking behavior[18] using validated questions adapted from the Youth Risk Behavior Survey (Kann et all, 2018.) Finally, we will assess satisfaction with game play and acceptability and feasibility of the intervention by collecting self-report data at the end of the game play period. All assessments will be conducted on a secured Qualtrics website with instructions from school program staff.

Study locations. Students will be enrolled from within the Seattle School District in Seattle, Washington. School program staff will select classes and teachers to participate in the study with an option to opt-out.

Participants, screening, and consent. In collaboration with community program staff at Seattle School District, an information letter describing the study will be provided to interested parents and adolescents. Letters will be sent home with each child and an announcement about the letter will be emailed to parents. If the participant is eligible and interested, they will be enrolled in the study. If a parent or participant does not want to participate in the study, they may choose to opt out by contacting the school program staff. Dr. Hieftje will call in through a live video-feed call through Zoom and provide a face-to face conversation with teens from classes that have been chosen by the school to participate in the study to describe the study and provide time for questions. Teens will also be provided Dr. Hieftje's phone number to call with any additional questions or clarification.

5. Genetic Testing N/A ☒

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.
   Adolescents ages 11-17 will be recruited into this study.

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 the focus groups and pilot-testing, inclusion/exclusion criteria are: participants must be 12-17 years of age and speak English. For the randomized controlled trial, participants must be between the ages of 11-15, Speak English, and be able to play a mobile app-based videogame and VR videogame (willing to sit with a smartphone or tablet computer and/or use a VR headset for 45-60 minutes/session to play the game). Eligibility will be determined by the research team.

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

   Eligibility will be determined by the research team. If a prospective participant meets the inclusion criteria, they will be eligible to participate in the project.

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 *Invite Only VR* may pose a potential psychological risk in that we address sensitive issues around tobacco use 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 substance use. 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. Kimberly Hieftje will provide consultation to the participant.

    Also the use of a virtual reality headset for the project may pose a slight physical risks for the participants in the form of dizziness, queasiness, seizures (about 1 in 4000 experience this effect), eye or muscle twitching, and faintness.

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.

To minimize possible physical risks associated with the project, per the health and safety manual for the virtual reality headsets, participants will not be allowed to use the virtual reality headsets while they are tired, sleep impaired, if they have digestive problems, are under emotional stress or anxiety or suffering from a cold, flu, headache, migraine or earache. Additionally, participants using the virtual reality headsets will be required to take a 10-15 min break for every 30 mins of game play.

Furthermore, throughout their gameplay experience, to help minimize risk participants utilizing the VR headsets will be asked about how they are physically feeling. If the participant's answer indicates that they are experiencing any of the adverse physical symptoms, the research staff will immediately stop gameplay.

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. Hieftje who will then determine if further consultation is required without divulging the name of the individual, if this appeared appropriate and necessary. Dr. Hieftje 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.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? Minimal risk
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

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 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, 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 that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB via the RNI submission process in IRES IRB 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.

Statistical procedures and models for analyzing data have been selected according to the research hypotheses being investigated and the types of data available. 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 statistical analyses will be conducted on an intention-to-treat sample using either SPSS/SAS statistical packages. Baseline characteristics will be analyzed using descriptive statistics.

We will evaluate the efficacy of Invite Only VR at reducing initiation of e-cigarette use (primary outcome). We will test the hypothesis that individuals who play Invite Only VR will be less likely to report the initiation of e-cigarette use in comparison to the control condition. We will conduct a longitudinal analysis using a linear mixed models approach to compare participants in the intervention group to participants in the control group on e-cigarette use from baseline across all follow-up assessments. An advantage of mixed models is that participants with missing data need not be excluded as all available data are used in estimating parameters. We will also use logistic regression models to determine if any relevant baseline variables are associated with rates of initiation of e-cigarette use (constructed as a binary outcome (Yes/No). We plan to evaluate the prognostic significance of a small set of predictor variables (e.g., knowledge, intentions, perceptions, attitudes, social norms, and self efficacy) and use them as covariates in the primary analysis.

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

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

B. DEVICES ☒

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

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*

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: 300 for sub-study 1; 400 for sub-study #2**
   a. Targeted for enrollment at Yale for this protocol: 300; 400
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: n/a

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

☒ Flyers	☐ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☐ 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:		

* 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

For sub-study #1

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 via posters and flyers located and circulated at the two community centers with which we have partnered. Potential participants will meet with the Research Assistant to discuss participation in the study. For the RCT, If the participant is interested, the Research Assistant will discuss the study with their guardian/parent and obtain informed written assent from the participant and written informed consent from their guardian/parent. For the focus groups, the Research Assistant will discuss the study with their guardian/parent and obtain verbal assent from the participant and verbal consent from their guardian/parent 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; particularly as they relate to avoiding tobacco use. 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.

In addition to paper forms for parental consent for participation in the randomized controlled study, we will also provide a web-based form for parents to review and electronically sign through Yale Qualtrics.

For sub-study #2

Participation in this study will be strictly voluntary, confidential and non-discriminatory. Participants will be enrolled while they are on-site at one of school classrooms in Seattle Schools. For the quasi-experimental study, information sheets will be provided to the adolescents and parents about the study.. If a parent does not wish their child to participate, they can call the designated school program staff to opt out. An email will also be provided later to all student's parents about the study as a second means of ensuring the letter reaches the parents. If a participant or their guardian/parent indicates that they do not wish to participate, there will be no further involvement in the study.

The PI from the research team (Dr. Hieftje) will Zoom in to each classroom to discuss the study with students over video and consent them into the research. In addition to the opportunity to contact the PI with questions during recruitment, students will have the time to ask questions regarding the study and will be provided with a phone number to speak with Dr. Hieftje directly if they desire. Parents will also be provided a phone number in the verbal consent sheet so that they may contact her directly with questions or more information.

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.

   Sub-study #1

   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 via posters and flyers located at the two listed community sites. 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; particularly as they relate to tobacco use. For the focus

groups we will employ waived signature of consent. Parents who do not wish for their children to participate will contact the project director. For the evaluation, we will obtain informed written assent from the participant and written informed consent from their guardian/parent. 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.

In addition to paper forms for parental consent for participation in the randomized controlled study, we will also provide a web-based form for parents to review and electronically sign through Yale Qualtrics.

Sub-study #2

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 school programs. For the quasi-experimental study, verbal information sheets will be provided to the adolescents and parents about the study with a waiver of documentation of consent .

The PI from the research team (Dr. Hieftje) will Zoom in to each classroom to discuss the study with students over video. Students will have the time to ask questions regarding the study and will be provided with a phone number to speak with Dr. Hieftje directly if they desire. Parents will also be provided a phone number in the verbal consent sheet so that they may contact her directly with questions or more information. Participants will be provided with an age-appropriate description of the study and told about what they might expect and may opt out if they desire. 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; particularly as they relate to avoiding tobacco use. If a participant or their guardian/parent indicates that they do not wish to participate, there will be no further involvement in the study. If a parent does not wish their child to participate, they can call Kimberly Hieftje (PI), who will then notify the school. Students may remove themselves when the experiment starts if their assent or parental consent has not been provided.

For students that have opted out of the study, they will work on other assignments provided by the teacher.

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; particularly as they relate to tobacco use. For focus groups, we will employ waived signature of consent. Parents who do not wish for their children to participate will contact the project director. For the randomized 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 Speaking Subjects will not be able to participate in this project.

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)*

☒ Entire Study (Note that an information sheet may be required.) – For focus group participation and sub-study #2.

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? *Name, Address, Telephone Number, Email Address*

2. How will the research data be collected, recorded and stored? All data collected from the assessments will be entered directly into the secure web-based system, OnCore, which is Yale's enterprise-wide data management system. Research staff will enter the data into the OnCore system. For the more sensitive information collected, the participant will enter these data. To assess acceptability and feasibility, directly following completion of the intervention, we will collect quantitative and qualitative data on the intervention participants' experiences of the game intervention.

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?

   Data will be stored in Yale's secured online data collection system, OnCore. Paper assessments will be kept in a locked filing cabinet in the PI's office.

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

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. Data collected in the study will reside in our computerized database and electronic storage mechanisms. All data analyses will be performed under approved HIC protocols.

6. 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.)

Potential benefits expected from the result of this research include a better understanding on how the use of videogame technology may influence health behaviors in young adolescents that impact their health and well-being. Specifically, this research will help to inform the sparse research available on the use of virtual reality to influence behaviors and social perceptions in adolescents.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   Not participating 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.

   We will compensate focus group participants and participants who participate in pilot testing with gift cards with monetary value of $25. Voice over participants will receive a gift card valued at $30.

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*

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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