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Clinical Research Protocol
VIP Smoking Cessation Intervention for Adults with Serious Mental Illness

Protocol Number:	
Version Date:	February 25, 2019
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Funding Organization:	Tobacco-Related Disease Research Program
Principal Investigator:	Name: Heather Leutwyler Telephone: Fax: E-mail:

Approval:

2/25/2019

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Heather Leutwyler with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

[redacted]

Protocol Title: **VIP Smoking Cessation Intervention for Adults with Serious Mental Illness**

[redacted]

2/25/2019

Investigator Signature *Date*

Heather Leutwyler, Associate Professor

Print Name and Title

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LIST OF ABBREVIATIONS

AE	adverse event
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
IRB	Institutional Review Board
PI	Principal Investigator
SAE	serious adverse experience

PROTOCOL SYNOPSIS

TITLE	VIP smoking cessation intervention for adults with serious mental illness
SPONSOR	Heather Leutwyler
FUNDING ORGANIZATION	Tobacco-Related Disease Research Program (TRDRP)
RATIONALE	Up to 95% of people with serious mental illness (SMI) smoke cigarettes. They are heavier smokers, have more severe withdrawal symptoms, lower quit rates, poorer health and die about 25 years earlier than those without SMI. Smoking is one of the most important modifiable risk factors for excess morbidity and mortality in the SMI population. Many smokers with SMI are reportedly motivated to quit, however success rates among these smokers remain low and evidence-based treatment targeting this vulnerable group is limited. While the evidence for the use of exercise as a smoking cessation aid in the general population is mixed, our team has data from several trials that suggest the use of a videogame-based physical activity program is an accessible and effective method to improve psychiatric symptoms, increase physical activity, decrease social isolation, and improve health among people with SMI. One strategy to improve smoking cessation outcomes is to provide treatments that mitigate abstinence-induced decrements (e.g., anxiety, cravings) while improving health outcomes. To address an urgent need to identify interventions that assist smoking cessation efforts, while contributing to improved health for people with SMI, the proposed PILOT two-arm randomized controlled trial (RCT) targeting 60 adults with SMI.
STUDY DESIGN	**We propose to conduct a pilot 2-arm RCT to examine the feasibility and potential efficacy of an application of our video-game based group physical activity intervention for smoking cessation in adults with SMI.**
PRIMARY OBJECTIVE	*Aim 1. Examine the feasibility and acceptability of a smoking cessation intervention tailored for adults with SMI.*

SECONDARY OBJECTIVES	*Estimate the efficacy of the VIP intervention group compared to the control group (sedentary video games, pharmacotherapy, and smoking cessation counseling) by smoking reduction, days of non-smoking, and 7-day point prevalence tobacco abstinence (PPA) at 6 and 12 weeks.* *Exploratory Aim 3. Determine whether participants in the VIP group have a greater reduction in the number and severity of psychiatric symptoms (measured by the Brief Psychiatric Rating Scale) compared to controls.*
NUMBER OF SUBJECTS	60
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 18 years and older, diagnosis of a SMI, Smoking at least five cigarettes per day for the past 6 months, Willingness to set a quit date, Not currently taking bupropion or using NRT, Current participant in the residential or day treatment program at Rypins with the intention to continue in the residential or day treatment program for at least the 12 week intervention period, Capacity to consent. Exclusion Criteria: Diagnosis of seizure disorder, history of anorexia/bulimia, undergoing abrupt discontinuation of ethanol or sedatives, other conditions that increase seizure risk (e.g., AV malformation, severe head injury, CNS tumor), Currently pregnant or breastfeeding, Planning to become pregnant during the study period, previous participation in the videogame-based physical activity intervention, Known medical conditions or other physical problems that need special attention in an exercise program (e.g. prior myocardial infarction, uncontrolled hypertension, history of angioplasty, history of angina, use of nitroglycerin to treat angina)
Intervention Group	Participants will play an active videogame using the Kinect for Xbox 360 game system (Microsoft, Redmond, WA), for 50-minutes three times a week for 12 weeks.
Control Group	Participants randomized to the control group will play sedentary videogames using the Xbox 360 game system (without the Kinect sensor) for 50-minutes three times per week for 12-weeks.
Study Procedures for both groups	Both groups will receive with smoking cessation counseling and pharmacotherapy (bupropion). Participants will be prescribed Bupropion sustained release (SR) two weeks before their quit date, as it takes 5 to 7 days to reach steady-state blood levels. The

	recommended dose of bupropion is 150 mg/day for three days, then 150 mg twice a day thereafter with treatment lasting at least 12 weeks.[44]
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The total time commitment is 12 weeks. Over the 12 weeks, participants will spend 48 hours engaged in the study. This time commitment includes 8 thirty-minute counseling sessions. In addition, participants will play videogames using the Kinect for Xbox 360 game system (Microsoft, Redmond, WA), for 50-minutes three times a week for 12 weeks, and 3 assessment visits at enrollment, 6 and 12 weeks that last up to 2 hours each. Upon completion of the 12 week program, there will be a 1-2 hour group interview.
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• Feasibility and acceptability
SECONDARY ENDPOINTS	• Smoking cessation and psychiatric symptoms
SAFETY EVALUATIONS	Incidence of adverse events
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study through Visit 12, an interim analysis for safety will be conducted by a data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	For Aim 1, number of sessions attended will be calculated and average rating of acceptability will be calculated. The analysis for the second and third AIMS will be carried out with multilevel regression analysis[51] to test the change over three assessments in success in smoking cessation (AIM 2), and number and severity of psychiatric symptoms (AIM 3). Change in these outcomes will be examined to test the difference in the linear change trajectories between the two arms of the study over three assessments from baseline through 12 weeks (also called the cross-level interaction between group and time).

Rationale for Number of Subjects	A primary purpose of the proposed pilot study is to estimate the effect of the intervention to obtain estimates that can be used in planning future studies with larger samples.[62] It is well known that only medium-to-large, or large effects can be detected using significance tests with samples as small as our proposed 60 participants. [63] Therefore, in addition to estimating and testing the change over time for each outcome, the observed effect sizes will be reported for the difference between the two groups at each assessment. Odds-ratios and differences in the proportion of successes will be reported for abstinence, and standardized differences (Cohen's d)[63] will be reported for psychiatric symptom severity, along with nonparametric bootstrapped, bias-corrected confidence intervals for all effects.

1 BACKGROUND

Smoking prevalence remains disproportionately high among adults with serious mental illness (SMI), and estimates suggest that between 50 and 95% of adults with SMI smoke cigarettes.[5,6] Compared to smokers in the general population, smokers with SMI are heavier smokers, have more severe withdrawal symptoms, lower quit rates, poorer health, and die about 25 years earlier.[1,2] Annually, more than 200,000 U.S. adults with SMI die of tobacco-related diseases, which account for nearly 40% of all annual tobacco attributable deaths.[7] In California, about half of all deaths among hospitalized adults with SMI are due to at least one of 19 diseases causally linked to tobacco use (e.g., cancer, respiratory diseases).[8] Smoking is one of the most important modifiable risk factors for the excess morbidity and mortality in the SMI population.[2] In addition, the economic burden from smoking is significant. Smokers with SMI spend almost a third of their monthly income on cigarettes, and the cost to society includes increased health care costs and work force absenteeism.[9] Individuals with SMI experience significant tobacco-related health disparities that warrant innovative intervention approaches to effectively treat nicotine dependence. Even though the motivation to quit smoking is high for smokers with SMI, their success rate is low.[10] Reasons for this discrepancy between motivation and success include limited access to effective treatment.[10] Treating tobacco use among adults with SMI is both a World Health Organization and TRDRP priority.

Evidence-based interventions for smokers with SMI include a combination of cessation counseling and pharmacology.[11] Despite evidence that combination therapy is an effective smoking cessation strategy for adults with SMI, this population continues to smoke at alarming rates.[12] For the general population of adult smokers, physical activity has been proposed as an aid for smoking cessation because it buffers psychological withdrawal symptoms and reduces cravings.[13] Evidence is mixed on whether increasing physical activity, either alone or in combination with other smoking cessation strategies has an effect on cessation success in adults without SMI.[13] Some reasons exercise interventions have failed to demonstrate an adequate effect size include: small samples, lack of intensity of the exercise intervention, and lack of adequate support for adherence to programs.[13]

Our team developed and pilot tested a videogame-based physical activity intervention to promote physical activity in adults with SMI. Our data suggest that the videogame-based physical activity intervention increased motivation and engagement in physical activity through group participation and the use of a fun exercise program.[1,14,15] **The use of a videogame-based group physical activity intervention developed for adults with SMI and applied for smoking cessation may be an effective, accessible, and a sufficiently intense intervention to increase smoking cessation success in adults with SMI.**

2 STUDY RATIONALE

Adults with SMI have greater *morbidity and mortality* than the general population. [16–18] Although there are increasingly better psychiatric treatment options and better responses to these treatments,[19,20] age adjusted mortality rates for adults with SMI are two times that of the general population.[21] Cigarette smoking is the major contributing factor to the high

prevalence of acute and chronic disease and disability among adults with SMI. [16,22] A recent report found that in California, half of all deaths of adults hospitalized for SMI were due to one of 19 diseases causally linked to tobacco use.[8] Adults with SMI are more likely to have stressful living conditions, low annual household income, and limited access to health insurance, health care, and help quitting smoking. All of these factors make it more challenging for adults with SMI to quit smoking.[2,6]

Despite evidence that effective cessation interventions for smokers with SMI include a combination of behavioral therapy and pharmacology, [11] they continue to smoke at alarming rates. Compared to a quit ratio of 52.8% in the general population, adults with a SMI have a quit ratio of 38.4%.[23] Reasons for poor success include: lack of treatment, misconceptions among patients that tobacco use decreases psychiatric symptoms, and mental health treatment settings that are not tobacco-free.[10] **Research is needed to develop effective smoking cessation interventions that are accessible, feasible, and acceptable for adults with SMI.**

Physical activity interventions and health benefits in people with SMI. Physical activity promotes better mental (i.e. depression and anxiety) and physical health outcomes.[24,25] Even short periods of low intensity physical activity can positively influence mental and physical health.[26] In a Cochrane review,[24] the efficacy of three physical activity RCTs (i.e. walking, combination of walking and jogging, or combination of weight training and aerobic training) in people with schizophrenia were evaluated. The authors concluded that the impact of these programs on health outcomes was mixed. One study provided evidence of improved fitness and all three studies showed psychological benefits (e.g., less severe psychiatric symptoms) from physical activity. However, RCTs that compared physical activity interventions with standard care failed to demonstrate changes in other health outcomes, such as body mass index (BMI) and blood pressure. Since standard physical activity interventions have failed to improve important health outcomes, more work is needed to understand what will support increased adherence to physical activity programs and improved outcomes in adults with SMI.

Smoking cessation, physical activity, and adults with SMI. For the general population of adult smokers, physical activity has been proposed as an aid for smoking cessation because it buffers psychological withdrawal symptoms and reduces the desire to smoke.[13] A recent Cochrane review[13] of 20 randomized controlled trials (RCTs) aimed at increasing physical activity, either alone or in combination with a smoking cessation intervention showed mixed results however, three studies did find an effect in favor of the intervention at the end of treatment.[27–30] In the study by Bock et al.,[27] 55 women were randomized to either a control group (n=23) which consisted of an 8-week program of cognitive behavioral therapy (CBT) along with a wellness program or to an intervention group (n=32) which received CBT plus twice weekly 1-hour yoga groups. Upon program completion (8 weeks), the intervention group had significantly greater odds of smoking abstinence when compared to individuals in the wellness group at 24 hours (47% vs 17%) and at seven days (41% vs 13).

Marcus et al.[28] conducted an RCT with 281 sedentary female smokers. The participants were randomly assigned to an intervention group (n=134) which consisted of a CBT smoking cessation program with vigorous exercise while the control group (n=147)

received a CBT smoking cessation program with equal staff contact time. The exercise program consisted of 3 supervised 50-minute exercise sessions per week. At 20 weeks after the quit day, the intervention yielded greater biochemically verified 7-day PPA than control (24.6% vs 13.6%), but no treatment effect was observed at 60 weeks. Poor adherence to the program (participants attended 67.3% of the exercise sessions) may be an indication that the program would be difficult to integrate into routine care.

Martin et al.[30] randomized 205 non hospitalized recovering alcoholics (92 women and 113 men) to one of 3 conditions: Standard treatment (ST) American Lung Association quit program plus nicotine anonymous meetings (n=70), behavioral counseling plus physical exercise (BEX; n=72), or behavioral counseling plus nicotine gum (BNIC; n=63). The exercise program consisted of cardiovascular activity, delivered in group or individual settings, once a week, for 4 weeks. The sessions lasted 15-45 minutes and participants exercised at 60-75% heart rate maximum. Verified self-report indicated that significantly more smokers in the BEX group quit by post-treatment (4 weeks) (60%) than in either BNIC (52%) or ST (31%).

The reasons most of the exercise interventions failed to demonstrate an effect size were: insufficient sample sizes, exercise sessions and support were not frequent or long enough, and poor adherence to the program.[13] In order to make a significant impact on smoking cessation, an exercise program needs to be offered multiple times a week, possibly in a group atmosphere, with sufficiently intense exercise to achieve at least 150 minutes of moderate activity per week. **The 3 programs that showed a significantly improved abstinence rate did not combine the program with pharmacotherapy.** The use of a videogame-based group physical activity intervention applied to smoking cessation may be an effective, accessible, and sufficiently intense method to increase the rates of smoking cessation success and tobacco related disease prevention in adults with SMI. Since standard smoking cessations interventions have failed to improve smoking cessation outcomes in adults with SMI, a novel intervention, like the one that will be tested in this RCT, is needed to facilitate increased adherence and improved outcomes in adults with SMI.

Videogame-based physical activity programs, physical activity and adults with SMI. Videogames with an interface that requires physical exertion to play, such as the Kinect for Xbox 360 game system (Microsoft, Redmond, WA) promote physical activity.[31] The Kinect for X-Box 360 system does not require the participant to use a controller. Instead, the participant uses their body to directly control the game. The Kinect sensor utilizes full-body tracking that recognizes the participant's body and mirrors movements in the game. [redacted] In 2011, the American Heart Association convened a scientific panel that examined whether videogame based physical activity improved health-related skills and health behaviors.[31] The panel included experts in health care, health promotion, behavioral sciences, technology, and game development. They concluded that videogames make physical activity more appealing and engaging for people of all ages and can increase daily activity levels. Videogame research demonstrated that as people become more involved and successful with active videogames, they developed skills that made it easier

for them to engage in activity and reported higher levels of physical and emotional well-being.[31] Furthermore, active videogames serve as a gateway to activities that lead to a more physically active lifestyle.[31]

Smoking cessation, pharmacotherapy, and adults with SMI. Clinical practice guidelines recommend combination strategies (e.g., behavioral therapy plus pharmacotherapy) to optimize quit rates.[11,32] Bupropion (Zyban) is effective for adults with SMI who smoke.[33] Bupropion acts on dopamine, norepinephrine, and nicotinic-cholinergic receptors, thereby decreasing cravings and withdrawal symptoms. A recent systematic review provides evidence that bupropion supports quit attempts.[34] Eight trials were pooled to determine whether the addition of bupropion to a range of interventions (e.g., cognitive behavioral therapy, support group) offered any additional cessation benefit. The addition of bupropion improved quit rates significantly in the medium term (median duration 3.5 months) and long term (median duration 11.75 months).[34] Bupropion is well-tolerated among smokers with current or past psychiatric disorders .[33] Among patients with schizophrenia stabilized on an adequate antipsychotic regimen, two meta-analyses concluded that bupropion for quitting smoking was well tolerated and more than doubled the likelihood of abstinence at end of treatment and 6-month follow-up .[11,35]

2.1 Risk / Benefit Assessment

The PI and other study personnel will make every attempt to preserve the confidentiality of participants. All personal identification will be separated from the data except on the master list, which will be kept locked in the PI's office at UCSF. In addition, participants will be encouraged to take frequent breaks to alleviate fatigue. If participants become uncomfortable during any part of the study, they may decline to do any set of tasks, or withdraw from the study entirely. The P.I. will maintain close contact with the primary clinician for each research participant while they are involved in the study to be alert to changes in clinical status. She will be available to all participants, family members, and clinicians for any observed concerns that arise regarding the study. In addition to minimizing a risk of musculoskeletal pain/injuries, we will discuss physical activity safety issues with the participants at the beginning of the study. The intervention is also designed for participants to gradually increase physical activity. The PI is a board-certified nurse practitioner and will assess as participants at enrollment as to suitability for the study. The PI will follow up with participants at 1 and 2 weeks after initiating the study medication and at each follow up visit. All study staff will complete training in Basic Life Support (BLS) including CPR and will update their certification every two years. In order to address potential for smoking withdrawal effects, all participants will receive smoking cessation counseling and the PI will maintain close contact with participants.

Effective physical activity programs and smoking cessation program for adults with SMI that can be done at a mental health facility are needed but not currently available.

3 STUDY OBJECTIVES

3.1 Primary Objective

Aim 1. Examine the feasibility and acceptability of a smoking cessation intervention tailored for adults with SMI.
Hypothesis 1: The VIP smoking cessation intervention will be feasible (defined as greater than 70% of participants attending 24 out of the 36 sessions) and acceptable (defined as greater than 70% of participants rating the intervention as acceptable).

3.2 Secondary Objectives

Exploratory Aim 2. Estimate the efficacy of the VIP intervention group compared to the control group (sedentary video games, pharmacotherapy, and smoking cessation counseling) by smoking reduction, days of non-smoking, and 7-day point prevalence tobacco abstinence (PPA) at 6 and 12 weeks.

Hypothesis 2: Participants randomized to the VIP group will achieve greater smoking reduction, days of non-smoking, and 7-day PPA than the control group at 6 and 12 weeks.

Exploratory Aim 3. Determine whether participants in the VIP group have a greater reduction in the number and severity of psychiatric symptoms (measured by the Brief Psychiatric Rating Scale) compared to controls.

Hypothesis 3: Participants in the VIP group will have a greater reduction in the number and severity of psychiatric symptoms than the control group at 6 and 12 weeks.

4 STUDY DESIGN

4.1 Study Overview

We propose to conduct a pilot 2-arm RCT to examine the feasibility and potential efficacy of an application of our video-game based group physical activity intervention for smoking cessation in adults with SMI. We will apply our intervention for smokers with SMI by creating the VIP intervention: **VI**deogame-based **P**hysical activity intervention (*50 minutes, 3X/week for 12 weeks = 36 sessions*) with smoking cessation counseling and pharmacotherapy (bupropion). Control group participants will engage in sedentary videogames (*50 minutes, 3X/week for 12 weeks = 36 sessions*) with smoking cessation counseling and pharmacotherapy (bupropion).

4.2 Primary Efficacy Endpoint

Feasibility will be measured with a count of sessions attended and with total minutes attended out of the possible total minutes of attendance. The GSR will monitor participants throughout the sessions and will document if a participant leaves the session early. Overall retention rates will be calculated from the beginning to the end of the intervention. Based on our prior studies of high retention, and prior studies using exercise intervention for smokers that generally had only < 60% adherence/retention, we anticipate the retention rate of the VIP intervention will be at least 70% who will complete at least 24 out of the 36 sessions. Failure of meeting this objective will call for a major revision of the retention protocol.

Acceptability will be measured with a questionnaire from our previous pilot studies. The questionnaire contains 7 questions with numerical ratings and open-ended responses. An example of two questions include: On a scale of 1 to 5, with 1 equal to "did not like it at all" and 5 equal to "liked very much", how enjoyable were the games? What was your favorite game and why? The acceptability questionnaire will be completed at weeks 6 and 12. In addition, we will measure acceptability by the number of participants approached who agreed to participate. We anticipate greater than 70% of the sample rating the intervention as acceptable (at least a 3 on a scale of 1-5).

4.3 Secondary Efficacy Endpoints

Tobacco reduction and abstinence will be assessed and verified at enrollment, 6, and 12 weeks. We will collect information on smoking reduction and days of non-smoking. We will ask about the number of cigarettes, even a puff, smoked in the past week (7-day abstinence) or use of any form of tobacco or alternative tobacco product e.g., e-cigarette or heat not burn. Consensus guidelines recommend use of 7-day PPA in cessation induction studies with smokers unmotivated to quit, who will be quitting at different time points in the trial. In addition, to verify self-report, abstinence will be measured by salivary cotinine level <15ng/ml. Salivary cotinine levels will be measured at enrollment, 6 and 12 weeks.

The number and severity of psychiatric symptoms will be assessed with the Brief Psychiatric Rating Scale (BPRS).[47] The BPRS consists of 16 items that are rated from 1 (not present) to 7 (extremely severe), and the items are summed for a total psychopathology score. The BPRS is one of the most widely used scales for assessing psychopathology and the reliability, sensitivity, and validity have been extensively examined.[48] The BPRS will be administered at enrollment, 6, and 12 weeks.

4.4 Safety Evaluations

Incidence of adverse events

5 SUBJECT SELECTION

5.1 Study Population

Subjects with a diagnosis of serious mental illness who meet the inclusion and exclusion criteria will be eligible for participation in this study.

5.2 Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
A diagnosis of a SMI*	Currently pregnant or breastfeeding
18 years and older	Diagnosis of seizure disorder, history of anorexia/bulimia, undergoing abrupt discontinuation of ethanol or sedatives, other conditions that increase seizure risk (e.g., AV malformation, severe head injury, CNS tumor)
Smoking at least five cigarettes per day for the past 6 months	
Willingness to set a quit date	*Planning to become pregnant during the study period*
Not currently taking bupropion or using NRT	*Previous participation in the videogame-based physical activity intervention*
Current participant in the residential or day treatment program at Rypins with the intention to continue in the residential or day treatment program for at least the 12 week intervention period	Known medical conditions or other physical problems that need special attention in an exercise program (e.g. prior myocardial infarction, uncontrolled hypertension, history of angioplasty, history of angina, use of nitroglycerin to treat angina)
Capacity to consent.	

* SMI is characterized by the American Psychological Association as distinct conditions that require routine management, produce functional impairment, and interfere with quality of life. Individuals that typically meet the criteria of SMI have illnesses that include schizophrenia, schizoaffective disorder, psychotic disorders, major depressive disorders, bipolar disorders, and borderline personality disorder.

6 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

After participants are enrolled and baseline data collection is complete, they will be randomized to the intervention or control group. We will generate assignment cards using a Stata program written to generate random assignment numbers for two equal groups of 5 in blocks of 10 cards. We will generate 60 cards that will assign participants into one of two groups in 6 blocks of 10 cards, using the uniform probability distribution with a cut of .5. At the randomization visit, the PD will enter the date, participant's name, and study ID (assigned at the screening and enrollment visit) consecutively in a randomization log, select the next numbered envelope, enter the randomization sequence number listed on the outside of the envelope, then open the envelope and enter the study group assignment contained on the card in the envelope on the randomization log. In case the enrollment is not sufficient to obtain the targeted 60 participants, 10 additional assignment cards (five randomly assigned into each of the two groups) will be used in order to reach the target number of 60.

7.2 Measures of Treatment Compliance

After the research assistants are trained, Dr. Leutwyler will observe the first two group sessions. The Project Director will randomly observe one control group and one intervention group session each month during each 12-week wave. After each observation, the Project Director will meet with the PI to discuss the observations to confirm the fidelity of the intervention. In addition, the length of the intervention and level of participants' engagement during the session will be recorded by the GSRs. Assigning one GSR to each group (intervention or control) ensures protocol fidelity. Supervision of the groups is necessary to determine participants' engagement and adherence.

The PI will monitor medication adherence through weekly medication record review and pill counts.

8 STUDY PROCEDURES AND GUIDELINES

Figure 1 at the end of this protocol outlines the study procedures and the study procedures are further described in section 8.1 below.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

8.1 Clinical Assessments

8.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at enrollment, 6 weeks and 12 weeks as well as at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

8.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at enrollment.

8.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Enrollment.

8.1.4 Procedures for both VIP intervention and Control Group Activities.

Study procedures for both VIP Intervention and Control Group activities.
Pharmacotherapy. After the participant is deemed medically appropriate, they will be provided with study medication, detailed information on possible adverse events related to use of the study medication, and a schedule for 12 weeks. Target quit date (TQD) for all participants will be set for 14 days from initiation of medications to allow for normal up-titration of bupropion. Participants will be prescribed Bupropion sustained release (SR) two weeks before their quit date, as it takes 5 to 7 days to reach steady-state blood levels. The recommended dose of bupropion is 150 mg/day for three days, then 150 mg twice a day thereafter with treatment lasting at least 12 weeks.[44] For participants that cannot tolerate the 300 mg dose due to side effects, Bupropion 150 mg/day will be an option.[45] All participants will have a follow-up visit in person or by phone with Dr. Leutwyler one and two weeks after initiation of bupropion to monitor for adverse effects (e.g. tachycardia, insomnia, nausea and vomiting), and reinforce adherence to medication. The PI will monitor medication adherence through weekly medication record review and pill counts.

Smoking Cessation Counseling. The project director will deliver the intervention and has a background in delivering counseling protocols for intervention studies. Counseling will consist of 8 individual sessions to be delivered in-person and telephone over 12 weeks. Sessions 1 and 2 meet weekly in-person prior to the target quit date, sessions 3 meets in-person on or within 1-2 days of the target quit date. Sessions 4 to 8 are follow-up calls starting 1 week following the quit date and every other week thereafter. Session 9 meets in-person. In-person sessions will be 30 minutes each, and follow-up calls will be 15-20 minutes in duration. The counseling intervention uses a cognitive-behavioral framework that aims to enhance commitment to abstinence, promote medical adherence, and increase behavioral skills for achieving and maintaining abstinence. Prior to the quit date, counseling will focus on developing an individualized quit plan through engaging participants to complete a set of brief questionnaires to gain self-understanding of reasons for smoking, concerns and benefits of quitting, identifying triggers or high risk smoking situations and corresponding coping strategies. Counseling at post-quit date will focus on managing withdrawal symptoms, mood management with discussions on increasing pleasant activities and strategies to reduce negative moods, adapting healthy lifestyles and weight control (exercise, nutrition), and increasing social support.

8.1.5 Study procedures For VIP intervention group only.

In addition to the medication and smoking cessation counseling, the VIP group participants will be introduced to the videogame-based physical activity intervention two weeks prior to their target quit date. The videogame-based physical activity intervention will be administered in accordance with our study protocol, which was created during our pilot work, to ensure consistency over time and across groups. Participants will play an active videogame using the Kinect for Xbox 360 game system (Microsoft, Redmond, WA), for 50-minutes three times a week for 12 weeks.

Each participant will have the appropriate amount of space in order to have full range of motion. Approximately six feet of free space between the participant and the X-Box Kinect sensor is needed. The Rypins house has a room that is large enough to accommodate a group of 5 participants while they engage in the intervention. The games offer a variety of levels and each group will start off at the beginner level. Some games, like Yoga, provide the participants with feedback about how to correct their body movements to correctly match the coach on the screen. Participants will be taught warning signs to be aware of while exercising (e.g., shortness of breath, dizziness). Participants will be encouraged to discontinue the game if they notice any exercise warning signs. A GSR will facilitate the weekly sessions. The GSR and project director will complete training in Basic Life Support including training in CPR and Dr. Souza will provide guidance with regard to safety based on American College of Sports Medicine exercise guidelines.

As in our pilot work, we will start each 12-week wave with bowling from the Kinect Sports DVD and then give the participants the option of 10 games to try for each additional session. All participants will eventually play the same 10 games. These games will include: Kinect Sports (bowling, baseball, volleyball, and skiing), Kinect Dance Central 2, Kinect Adventures (River Rush and 20,000 Leaks), Twister, and Kinect Your Shape Fitness Evolved (Yoga and Body Focus Workouts). Consistent with our previous and ongoing studies, we will start with bowling because it is an activity most participants have watched or tried in the past. In addition, according to our previous participants, it is an easy game to learn and to become more adept at playing. All of the games were chosen based on feedback from previous participants and research staff experiences playing the different games in groups of people with schizophrenia. The games provide a variety of upper and lower body activities and promote coordination and balance; aerobic capacity, and strength and flexibility. Participants will take turns playing the games and the amount of time played per turn will be equal across group members. Some games, such as volleyball and skiing, allow for multiplayers at one time. Participants will start off the 12-week sessions with single player turns so that they can learn how to play the games. As the participants become more adept at the games, multiplayer games will be encouraged for longer periods of play time and more frequent turns.

8.1.6 Study procedures For Control group only.

In addition to the medication and smoking cessation counseling, the control group participants will be introduced to the sedentary videogames two weeks prior to their target quit date. Participants randomized to the control group will play sedentary

videogames using the Xbox 360 game system (without the Kinect sensor) for 50-minutes three times per week for 12-weeks. A GSR will facilitate the weekly sessions. We will give the participants the option of 10 games to try. All participants will eventually play the same 10 games. These games will include: Family Feud, The Price is Right, Cars Race-O-Rama, Family Game Night (Connect 4, Yahtzee, Life, Jenga, Clue), Wheel of Fortune, and PacMan. Participants will play the games seated with a remote control wireless device in a group of 5 participants.

8.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9 EVALUATIONS BY VISIT

9.1 Enrollment visit

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history.
5. Record concomitant medications.
6. Record the number of cigarettes, even a puff, smoked in the past week (7-day abstinence) or use of any form of tobacco or alternative tobacco product e.g., e-cigarette or heat not burn.
7. The number and severity of psychiatric symptoms will be assessed with the Brief Psychiatric Rating Scale (BPRS).
8. We will also collect data from all participants about the following variables to begin to determine the impact on additional clinical outcomes including: self-report of physical activity with the Yale Physical Activity Scale,[49] self-report of overall health (PROMIS global health measure), BMI, blood pressure, and waist circumference.
9. Participants will be given a physical activity monitor to wear for 1 week at enrollment.
10. Participants will be prescribed Bupropion sustained release (SR). The recommended dose of bupropion is 150 mg/day for three days, then 150 mg twice a day thereafter with treatment lasting at least 12 weeks.[44] For participants that cannot tolerate the 300 mg dose due to side effects, Bupropion 150 mg/day will be an option.[45]
11. Schedule subject for follow up visit with Dr. Leutwyler for one and two weeks after initiation of bupropion to monitor for adverse effects (e.g. tachycardia, insomnia, nausea and vomiting), and reinforce adherence to medication.
12. Randomize subject to intervention or control group.

13. Provide subject with a schedule for the next 12 weeks.

9.2 6-week Assessment

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Record any hospitalizations for psychiatric or medical reasons.
4. Update demographic form, concomitant medication form, and medical history form.
5. Record smoking cessation information: We will collect information on smoking reduction and days of non-smoking. We will ask about the number of cigarettes, even a puff, smoked in the past week (7-day abstinence) or use of any form of tobacco or alternative tobacco product e.g., e-cigarette or heat not burn. In addition, to verify self-report, abstinence will be measured by salivary cotinine level <15ng/ml. Salivary cotinine levels will be measured at 6 and 12 weeks.
6. The number and severity of psychiatric symptoms will be assessed with the Brief Psychiatric Rating Scale (BPRS).
7. We will also collect data from all participants about the following variables to begin to determine the impact on additional clinical outcomes including: self-report of physical activity with the Yale Physical Activity Scale,[49] self-report of overall health (PROMIS global health measure), BMI, blood pressure, and waist circumference.
8. Participants will be given a physical activity monitor to wear for 1 week.

9.3 12-week Assessment

1.Record any Adverse Experiences.

2. Concomitant medications review.
3. Record any hospitalizations for psychiatric or medical reasons.
4. Update demographic form, concomitant medication form, and medical history form.
5. Record smoking cessation information: *We will collect information on smoking reduction and days of non-smoking.* We will ask about the number of cigarettes, even a puff, smoked in the past week (7-day abstinence) or use of any form of tobacco or alternative tobacco product e.g., e-cigarette or heat not burn. In addition, to verify self-report, abstinence will be measured by salivary cotinine level <15ng/ml. Salivary cotinine levels will be measured at 6 and 12 weeks.
6. The number and severity of psychiatric symptoms will be assessed with the Brief Psychiatric Rating Scale (BPRS).
7. We will also collect data from all participants about the following variables to begin to determine the impact on additional clinical outcomes including: self-report of physical activity with the Yale Physical Activity Scale,[49] self-report of overall

health (PROMIS global health measure), BMI, blood pressure, and waist circumference.

8. *Participants will be given a physical activity monitor to wear for 1 week.*
9. Conduct focus group interview with control and intervention groups separately.

9.4 Early Withdrawal Visit

1. Record any Adverse Experiences.
2. Concomitant medications review.
3. Record any hospitalizations for psychiatric or medical reasons.
4. Update demographic form, concomitant medication form, and medical history form.
5. Record smoking cessation information: We will collect information on smoking reduction and days of non-smoking. We will ask about the number of cigarettes, even a puff, smoked in the past week (7-day abstinence) or use of any form of tobacco or alternative tobacco product e.g., e-cigarette or heat not burn. In addition, to verify self-report, abstinence will be measured by salivary cotinine level <15ng/ml. Salivary cotinine levels will be measured at 6 and 12 weeks.
6. The number and severity of psychiatric symptoms will be assessed with the Brief Psychiatric Rating Scale (BPRS).
7. We will also collect data from all participants about the following variables to begin to determine the impact on additional clinical outcomes including: self-report of physical activity with the Yale Physical Activity Scale,[49] self-report of overall health (PROMIS global health measure), BMI, blood pressure, and waist circumference.

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.

Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

10.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up

- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to week 6) should have an early discontinuation visit. Refer to Section 10 for early termination procedures. Subjects who withdraw after week 6 but prior to week 12 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a

Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

13 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

13.1 Data Sets Analyzed

All eligible patients who are randomized into the study and begin the 12-week program will be included in the safety analysis.

13.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by group: race, gender, age, height and weight.

13.3 Analysis of Primary Endpoint

For Aim 1, number of sessions attended will be calculated and average rating of acceptability will be calculated.

13.4 Analysis of Secondary Endpoints

The analysis for the second and third AIMS will be carried out with multilevel regression analysis[51] to test the change over three assessments in success in smoking cessation (AIM 2), and number and severity of psychiatric symptoms (AIM 3). Change in these outcomes will be examined to test the difference in the linear change trajectories between the two arms of the study over three assessments from baseline through 12 weeks (also called the cross-level interaction between group and time).

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to the intervention.

13.5 Sample Size and Randomization

A primary purpose of the proposed pilot study is to estimate the effect of the intervention to obtain estimates that can be used in planning future studies with larger samples.[62] It is well known that only medium-to-large, or large effects can be detected using significance tests with samples as small as our proposed 60 participants. [63] Therefore, in addition to estimating and testing the change over time for each outcome, the observed effect sizes will be reported for the difference between the two groups at each assessment. Odds-ratios

and differences in the proportion of successes will be reported for abstinence, and standardized differences (Cohen's d)[63] will be reported for psychiatric symptom severity, along with nonparametric bootstrapped, bias-corrected confidence intervals for all effects.

14 DATA COLLECTION, RETENTION AND MONITORING

14.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper case report form (CRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number.

For paper CRFs: If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

14.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

14.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis*For paper studies:* Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

14.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

14.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

14.6 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number will identify all study subjects on CRFs and other documentation submitted.

15 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

15.1 Protocol Amendments

Any amendment to the protocol will be written by the Principal Investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

15.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information)

will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

15.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

15.4 Publications

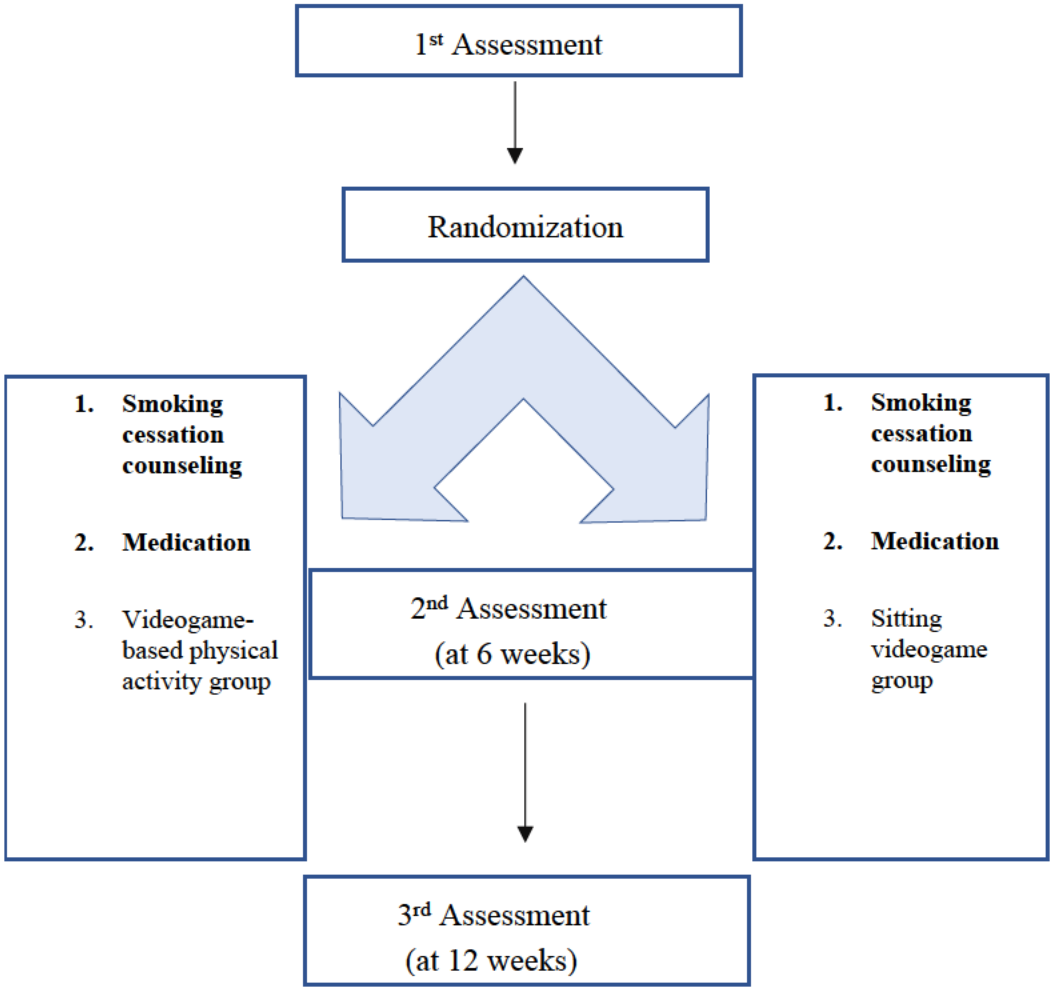
The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

15.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

FIGURE 1


1st Assessment
Randomization
1. Smoking cessation counseling
2. Medication
3. Videogame-based physical activity group
1. Smoking cessation counseling
2. Medication
3. Sitting videogame group
2nd Assessment (at 6 weeks)
3rd Assessment (at 12 weeks)