STUDY PROTOCOL

TRIAL OF INTEGRATED SMOKING CESSATION, EXERCISE AND WEIGHT MANAGEMENT IN SERIOUS MENTAL ILLNESS

Johns Hopkins IRB00072510 NCT02424188

Protocol notes

Edits to the protocol, all made prior to data analysis, are as follows:

Date: March 4, 2017 Version 1.1
i. Study sites updated
ii. Inclusion criteria updated: use of alcohol screener AUDIT, inclusion of mini-cigars, and removal of requirement for Fagerstrom
iii. measures of alcohol use updated

Date: May 29, 2020 Version 1.2
iv: Clarified that accelerometers were not used, 24-month data collection not obtained
v. Clarified that study physicians prescribe smoking cessation pharmacotherapy
vi. Due to updated research methods in literature, included sensitivity analysis using carbon monoxide (CO) <6 ppm
vii. Clarified use of cotinine and anabasine to supplement CO for biochemical verification of smoking abstinence
viii. Clarified secondary analyses on continuous abstinence
ix. Included exploratory analysis on reduction in smoking

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TRIUMPH Trial Protocol

1. ABSTRACT Persons with serious mental illness (SMI) have three times higher mortality rates than those without SMI, [1-5] primarily due to cardiovascular disease (CVD). [6-9] Tobacco smoking is the single largest contributor to CVD and preventable death in SMI. [5,10-13]Although U.S. smoking rates have declined dramatically, smoking persists at epidemic levels in SMI, affecting an estimated 53% or 6 million adults, higher than the U.S. prevalence in 1965. [14,15] While adults with SMI have markedly higher prevalence of all American Heart Association (AHA) targeted CVD risk behaviors than the general population: smoking; physical inactivity; unhealthy diet and obesity; smokers with SMI have 40% higher probability of a CVD event in 10-yrs than SMI non-smokers. [16-20]

The vast majority of smokers with SMI state they would like to quit. [21-23] Combination pharmacotherapy and behavioral treatment increases abstinence rates in trials, but has not been tested or widely used in community settings. [24,25] Almost all trials of cessation aids to-date in SMI target selected samples of those willing to quit right away, [26-30] excluding the less motivated. Moreover, weight gain may accompany smoking abstinence, and obesity is already widespread in SMI. [17,31,32] Exercise may improve nicotine withdrawal symptoms and reduce weight gain during a cessation attempt, [33-35] but studies of exercise with standard smoking cessation treatment are lacking in SMI. With extraordinarily high burden of all the CVD risk behaviors, combined health behavior change interventions relevant to a broad spectrum of SMI are urgently needed, especially in those who smoke.

The objective of this study is to develop and test an innovative, scalable intervention delivered in a community mental health organization setting that builds on smoking cessation interventions shown to be effective in trials, and aims to promote prolonged smoking abstinence, improved physical activity and weight control.

The TRIUMPH Trial is a community mental health organization-based, two-arm clinical trial that will test the hypothesis that an 18-month comprehensive, practical tobacco smoking cessation program integrating exercise and weight counseling will be superior to a treatment as usual (TAU) control in achieving prolonged smoking abstinence, physical fitness and weight maintenance. We will enroll 220 adults with SMI attending community mental health organizations in Maryland, who are current tobacco smokers expressing interest in quitting. We will stratify by readiness to set a quit date within 1 month or 6 months and randomly assign participants to receive: 1) TAU with referral to a quit line or 2) the 18-month intervention that will include: i) group and individual smoking cessation and weight management counseling by a health coach and tailored to participants' readiness to quit; ii) pharmacotherapy with either varenicline +/- nicotine replacement therapy, or bupropion + nicotine replacement therapy (NRT), prescribed in the community clinic; iii) group exercise and gym access; and iv) text messaging supporting health behavior change. We propose the following Aims:

2. SPECIFIC AIMS

Primary Aim: Test the hypothesis that TRIUMPH intervention participants will have higher rates of biochemically validated, 7-day point-prevalence smoking abstinence at 18 months than TAU participants.

Secondary Aims:

1. Determine the effect of the TRIUMPH intervention compared to TAU on other CVD risk behaviors and factors:
   a. Continuous smoking abstinence;
   b. Weight and Body Mass Index;
   c. Physical fitness with 6-minute walk test;
   d. Healthy diet by self-report;
   e. 10-year risk of cardiovascular events with the Global Framingham Risk Score;
2. Determine the effects of the TRIUMPH intervention on patient-reported and other outcomes: health status (SF-12); quality of life (Euroqol); psychiatric symptoms (BPRS); and acute care visits and hospitalizations;
3. Evaluate potential mediators of outcome (e.g., intervention attendance, text-messaging use, quit attempts, pharmacotherapy), and explore outcomes in selected subgroups of interest at baseline (e.g., those willing to set a quit date in 1 month, psychiatric diagnosis).
4. Assess costs per participant and cost-effectiveness incorporating long-term changes in CVD risk.
6. Assess factors that could facilitate implementation, and plan for future implementation and dissemination.

Improving smoking abstinence, physical activity, diet and weight is critical to decrease premature CVD mortality in SMI, and will require innovative, integrated interventions in community settings. The TRIUMPH Trial will test such an approach that reaches a broad range of smokers with SMI and is practical to implement.

3. BACKGROUND AND SIGNIFICANCE

Public health burden of tobacco smoking in persons with SMI

Nicotine dependence remains epidemic in adults with SMI, with smoking prevalence and resulting smoking-related mortality 2 to 5 fold higher than in the general population. [14,36-44] One provocative estimate suggests 45% of all cigarettes in the US are sold to those with a mental illness. [36] Compounded by the strikingly higher prevalence of all CVD risk factors in SMI, [45,46] smoking represents a major, neglected public health problem in this vulnerable population. [12,25,47]

Benefits of smoking cessation

Smoking cessation dramatically reduces CVD mortality. After only 1 year of abstinence, myocardial infarction risk is reduced by 50%, and cessation in mid-life abrogates 90% of smoking-associated mortality risk. [48-50] Smoking cessation treatments tailored to those with SMI are needed. [47]

Short-term interventions for smoking cessation in SMI.

A recent Cochrane review[24] based largely on trials conducted by Drs. Evins and Cather, [26,27,29,51-54] found pharmacologic + behavioral interventions effective and behavioral treatment alone ineffective for smoking cessation in schizophrenia. The 2009 Schizophrenia PORT guidelines, [55,56] for the first time recommended pharmacotherapy (bupropion +/- NRT) + behavioral treatment for those wanting to quit. [26,27,29,51-54,57,58] Since the PORT, varenicline has been found effective for abstinence and well-tolerated in smokers with schizophrenia, bipolar disorder and depression(B1f). [24,29,30,59-68] While pharmacotherapy has been found to be effective for smoking cessation in major depressive disorder (MDD), including a large study in depressed smokers by Dr. Evins, [69] more work is needed in schizophrenia, bipolar disorder and recurrent MDD, consistent with SMI. The planned intervention is appropriate for the range of diagnoses included in SMI.

Smoking is a chronic illness

Relapse rates are high shortly after discontinuing pharmacotherapy, [24] with some trials reporting 50% relapse by 3 months, most occurring within 2 weeks. [51] The average smoker makes 5 attempts before sustained abstinence, [70] so multiple tries after relapses should be expected and encouraged. This 18-month trial will address nicotine dependence as a chronic relapsing disorder in SMI.

Maintenance interventions for smoking cessation in SMI. Following a successful open trial of a 52-week maintenance intervention, [71] Drs. Evins and Cather recently completed the first RCT of maintenance smoking cessation treatment in schizophrenia and bipolar disorder (Figure 1). Among 203 smokers, the 43% attaining ≥ 14-day continuous abstinence at week 12 of an open phase intervention with varenicline and cognitive behavioral therapy (CBT) were randomized to 40 wks varenicline + CBT or placebo +CBT. Maintenance therapy tripled abstinence rates compared to control; 28% of the original sample was abstinent at 1 year (Figure 1). [61,67] Of those abstinent at week12, 60% randomized to active treatment were abstinent at 1 year. (data not shown) After discontinuation of pharmacotherapy at 1 year, half relapsed, supporting conceptualization of tobacco dependence a chronic condition in SMI, even after sustained abstinence. This informs our planned 18-month intervention.

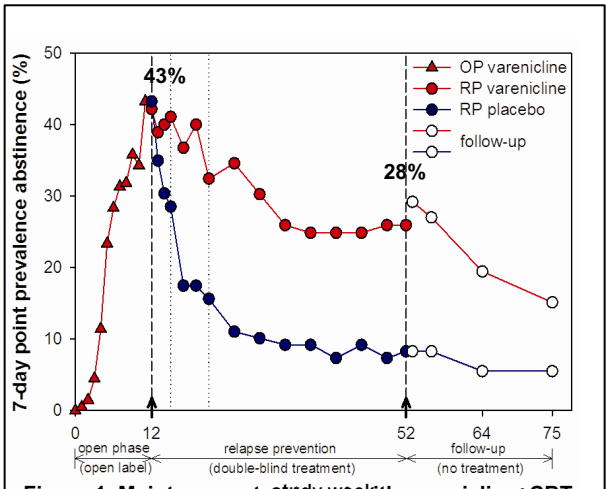

Figure 1. Maintenance treatment with varenicline+CBT. First 12 weeks open phase (OP) varenicline +CBT, those abstinent randomized to 40 weeks of varenicline + CBT vs. placebo and CBT for relapse prevention (RP); 52 to 76 weeks followed off treatment.

Dispelling myths about smoking cessation and SMI

Persons with SMI do want to quit smoking. A recent study found 77% of mental health clinicians believe an important barrier to intervention is that SMI patients are not interested in quitting, [72] however evidence shows the opposite –persons with SMI are at least as likely to want to quit as those in the general population, with 2/3 to 80% wanting to quit. [23] About half want to quit within 6 months and an additional ¼ or more endorse being ready in 30 days[21-23], categories which essentially correspond to the Transtheoretical Model contemplation and preparation stages. [73-75] Yet, few providers ask patients about smoking cessation or feel comfortable providing it, contributing to the abysmally low rates of receiving guideline-concordant treatment in SMI. [72,76-79] The proposed trial will test and implement comprehensive smoking cessation treatment in the community.

Pharmacotherapy for smoking cessation is safe in SMI

While initial trials excluding SMI reported few psychiatric adverse events, uncontrolled case reports alarmed the field. [80-82] However, now, controlled trials, including those conducted by Dr. Evins (B1e) [67] and a new, large meta-analysis in those with and without SMI find varenicline is not associated with increased psychiatric adverse events in smokers with psychiatric illness. [62,63,83-85] Bupropion combined with or without NRT has also been shown to be safe in SMI. [24,26,51,71,86-88]

Increasing motivation to quit smoking in SMI

Dr. Cather studied smokers with SMI who were either not interested in quitting or not ready to quit in 30 days. [89] After 4 weeks of motivational enhancement group sessions, 42% moved from pre-contemplation to being ready to take action to quit (i.e., set a quit date within 30 days). This motivational approach forms the basis for part of the TRIUMPH intervention. [89,90] (B3f6).

Peer support and smoking cessation in SMI

Peer support is well established in addiction treatment and has assumed an increasing role in mental health services. [91] Peer support may be particularly helpful in quitting smoking because of smoking's social nature. [92] Dr. Dickerson is leading a R34 to pilot a peer program to enhance a smoking cessation intervention for SMI. Although not the main focus of this study, we will capitalize on her expertise and include visits by her peer mentors and videos from Dr. Cather's patients who have quit.

Burden of other CVD risk behaviors: Overweight and obesity are epidemic in SMI, particularly in women, where 60% are obese. [18,93-95] Physical inactivity and unhealthy diet contribute. The vast majority of SMI take ≥1 long-term psychotropic, yet many drug classes cause weight gain, in part from increased appetite. [96-101]

Physical inactivity is prevalent in SMI

Dr. Daumit reported persons with SMI report 50% higher leisure time inactivity than the general population. [19] Her accelerometry study showed only 4% with SMI met recommended moderate to vigorous physical activity in bouts of ≥10 minutes. [102] Unhealthy diet is reported in SMI with some studies reporting higher fat and lower fruit and vegetables and others higher overall caloric intake. [103-105]

Weight loss and physical activity interventions for SMI. Lifestyle intervention trials are effective in the general population, yet systematically exclude SMI. [106-112] Until recently, a few published trials of weight loss in SMI showed success; most focused on diet changes and were short-term. [113-119] Dr. Daumit is an expert in developing and testing state of the art weight and exercise interventions in SMI. [120-122] She led an exercise pilot study in 93 with SMI showing improved fitness on treadmill testing for those attending at least 2/3 of exercise classes. [123,124] She recently completed ACHIEVE, a 10-site RCT of a weight loss intervention with 291 participants in PRPs, demonstrating overweight and obese adults with SMI can achieve and maintain clinically significant weight loss (7 lbs.) with an 18-month tailored diet and physical activity intervention. [125] ACHIEVE is the first large, long-term behavioral weight loss RCT in SMI, and distinct from most general population trials[107,109,110,112,126] where weight loss peaks at 6 months with regain later, participants continued to lose over 18-months. This persistent weight loss provides insight about how it may take longer for some SMI to change behavior, and supports addressing CV risk behaviors as chronic conditions requiring continued treatment. We will model weight management methods and exercise classes in the planned trial on our success in ACHIEVE.

Weight gain with smoking cessation[31] adds to the already high CVD risk in persons with SMI, who are

obese / overweight on average before quitting. [16] In Dr. Evins' study, those who attained 14-day point-prevalence abstinence at week 12 vs. those who did not, gained 6.9 lbs. compared with 0.5 lbs. [67] ($p<0.05$). Concern over weight gain is a barrier to smoking cessation, [127-130] and is likely a valid worry among adults with SMI compounding existing issues related to obesity. Some evidence shows combining smoking cessation with either weight counseling or exercise can aid smoking cessation, withdrawal symptoms and weight control. [131]

Exercise and smoking cessation

Exercise acutely reduces cravings and withdrawal symptoms such as negative mood, [34,35] and is associated with lower relapse risk. [132] While mechanisms are not certain, exercise may serve as a substitute behavior for smoking or as an alternative reinforcer. [133] Importantly, exercise may reduce post-cessation weight gain, [33] a critical issue for overweight or obese SMI smokers. Exercise has not been incorporated into a smoking cessation program for SMI. The proposed intervention will combine the PIs' expertise in individual behavior change in the areas of smoking cessation, healthy weight, and exercise.

Text messaging for health behavior change

Health information technologies such as mobile phones are evolving rapidly and by providing supportive messages, reminders, prompts to self-monitor and tailored automatic feedback shows promise for improving health behaviors. [134] Text-based messaging could be a cost-effective method to disseminate health behavior interventions on a large scale. A small number of text messaging interventions have been developed to promote smoking cessation and have shown to be effective in the general population. [135-141] This approach has not been applied to smoking cessation in persons with SMI, though studies indicate that given appropriate opportunity and training, many individuals with SMI can use mobile phone technologies successfully. [142,143] Dr. Daumit piloted a text messaging intervention for weight loss in SMI at a psychiatric rehabilitation program. Of 14 completing the 4-month intervention to-date, 2/3 responded to 75% or more of daily text prompts to report step-counts, weight, and sugar beverage intake. Initial results show weight loss correlated with higher responses to step count texts. Text messaging support will be integrated into the study intervention.

Persons with SMI are at extremely high risk for CVD morbidity and mortality; poor health behaviors, led by tobacco smoking, are chief causes. Even while, nationally, smoking rates are dropping, nicotine addiction is an entrenched problem for at least half of SMI adults, and rates of guideline-concordant cessation treatment are minimal. Drs. Evins and Cather have led influential clinical trials showing efficacy of combined pharmacologic and behavioral treatments for smoking cessation in SMI, including for long-term abstinence. However, interventions delivered by community providers and expanded to all smokers with SMI who want to quit need testing. The relation of weight gain to smoking cessation, potential beneficial effects of exercise on abstinence, importance of weight control and physical activity for CV health, and evidence from Dr. Daumit's work that long-term weight loss interventions are successful in SMI, provide strong rationale for addressing smoking cessation, weight control and exercise in an integrated 18-month intervention for SMI in community settings. Unless effective interventions are tested, this population will continue to lag far behind the nation in CVD goals, and disparities will likely persist if not worsen. If the CV risk behaviors that the trial aims to improve could be applied widely to the 6 million with SMI who smoke in the US, tens of thousands of lives could be saved. [4,144-146]

4. DESIGN SUMMARY

The core design is a randomized, two-arm, parallel, multi-site clinical trial. Inclusion/exclusion criteria were chosen to enroll a population with chronic mental illness who are active smokers with interest in quitting and who may safely participate in a smoking cessation and weight management intervention including smoking cessation group classes with either of two study medications to assist in smoking cessation, individual sessions, texting support program, and moderate intensity exercise. All interested mental health consumers will be screened for eligibility at two organizations; Johns Hopkins Bayview Adult Psychiatry Outpatient Program and Family Services, Inc. Two hundred and twenty adult participants completing screening will be enrolled and randomized to the TRIUMPH intervention or usual care. Intervention participants will receive group and individual smoking and weight management sessions and exercise program. Follow-up data collection will occur at 6, 12, 15, and18 months from baseline. The primary outcome variable will be 7-day point-prevalence smoking abstinence to be assessed at 18 months.

Randomized groups:
Control condition: Those assigned to the control group will receive usual care and will also receive referral to a telephone smoking quit line, a list of exercise resources and the NHLBI brochure Aim for a Healthy Weight. They will also receive a quarterly health newsletter.

Active intervention: Those assigned to the intervention group will receive the 18-month, TRIUMPH intervention, consisting of 1) group and individual smoking cessation and weight management counseling tailored to readiness to quit with a health coach; 2) state-of the-art pharmacotherapy with varenicline with or without nicotine replacement therapy (NRT) or bupropion with NRT prescribed in their community clinic; 3) text messaging integrated to support health behavior change; and 4) group exercise and supported gym access.

5. STUDY POPULATION AND ELIGIBILITY

The study sites are Johns Hopkins Bayview and East Baltimore Campuses Adult Psychiatry Outpatient Program, Keypoint Inc,. psychiatric day programs and outpatient clinics. PRPs have SMI patients attending regularly 3+ days/week and ample space for on-site group sessions and physical activity classes. Approximately 4,800 persons with mental Illness attend these programs.

We will enroll 220 adults with SMI who report nicotine dependence with a Fagerstrom Test for Nicotine Dependence (FTND) [147] score of ≥ 5 and are either interested in setting a quit date within 6 months (contemplation) or within the next 30 days (preparation). Based on Maryland Mental Hygiene data and Bayview reports, approximately 50-65% of the mental health consumers in our sites have nicotine dependence. Most consumers in the sites receive Medicaid and/or Medicare. Across the two sites, approximately 50% are women, 40% are African Americans, and mean age is 45 years. Approximately 40% have schizophrenia-related diagnoses; with bipolar disorder and depression each approximately 30%. An important goal of TRIUMPH will be generalizability across populations of SMI served in the community; thus eligibility criteria are broad with exclusion criteria mainly related to safety (Table 1).

Table 1. Eligibility Criteria
▪Age 18 and older
▪SMI– schizophrenia, schizoaffective disorder, bipolar disorder, or recurrent major depression meeting criteria for serious mental illness
▪ Daily cigarette smoking (or any smoked tobacco product e.g., mini-cigars, cigarillos) for at least the past 6 months (on days that smoked tobacco products were available)
▪On stable psychotropic medication for mental illness for at least 30 days (i.e. antipsychotic medication for those with schizophrenia spectrum illness, mood stabilizer for those with bipolar disorder)
▪Competent and willing to give informed consent
▪Completion of baseline data collection
▪Willing to participate in the smoking cessation intervention that includes combination of evidence-based behavioral (group and individual sessions) and pharmacotherapeutic smoking cessation aids ▪Interested in quitting smoking within six months
Exclusion criteria
▪ Serious cardiovascular event within the past 6 months (e.g. myocardial infarction, stroke)
▪ Serious unstable medical condition which limits life expectancy
▪ Review by treating psychiatrist required for those inpatient psychiatric hospitalization within six months of enrollment.
▪Review by treating physician (and anticonvulsant required) for those with seizure disorder with seizure in past six months. Review by treating physician with anticonvulsant or dose adjustment required for those taking medications that lower seizure threshold (e.g., clozapine >= 500mg).
▪ Pregnant, breastfeeding, or planning a pregnancy during study period.
▪ Active substance use disorder, alcohol use disorder, or problem drinking (more than 14 drinks per week for women, more than 21 drinks per week for men)
▪ Planning to leave mental health program or move out of geographic area within 18 months

6. RECRUITMENT

Recruitment, tracking and retention are facilitated because patients come on-site to the day programs or to mental health clinics regularly. In the day programs, we will present at regular consumer and staff meetings and will widely distribute brochures and posters. We will work with rehabilitation staff to identify potential participants by reviewing their list of program attendees with them. We plan to mail letters to potentially eligible consumers to tell them about the study. Rehabilitation counselors and mental health clinic staff may mention the trial to their consumers. Interested individuals will be directed to contact us by phone or in person at the day program or clinic. We may show informational videos about the study to potential partcipants. Study staff will be at the rehabilitation sites to discuss the study with any interested consumers. In outpatient clinics, we will work closely with leadership to engage providers to refer patients, and distribute flyers and brochures. Study team members will be on-site at clinics for potential participants to discuss interest in the study. We also will conduct and participate in health fairs about non-smoking, and healthy weight and exercise where study team members will be available to discuss the study for those interested.

Our assumptions are 1) 50-65% of consumers smoke, 2) at a minimum 60% will want to quit, and 3) all day program attendees and at least 75% of clinic attendees meet SMI criteria (from site data). Estimations are that of these, at least 25% will be interested in the trial, meet other inclusion criteria, and enroll, with a resultant yield of 5.8-7.5% of all site consumers. In ACHIEVE, 40% of all overweight /obese consumers at study sites enrolled (higher than the 25% we project in TRIUMPH). Other programs expressed interest in the proposed trial, and if needed, we could include another facility to increase recruitment. Enrollment and retention of a diverse study population are high priorities. Previous research have found recruitment yields a population similar to the site's underlying race and gender distribution; our studies have had approximately 40% African Americans and 50% women. [122,124,125] Strategies will be implemented to review each aspect of the trial (e.g., recruitment materials) with an eye towards ensuring minority enrollment, and track demographics during recruitment, adjusting procedures if needed.

Participant retention is an extremely high priority. We will use strategies successful in the teams' studies. In addition to maintaining strong participant rapport, we collect and review contact information throughout and will ask for relatives /friends' contacts who can facilitate communication if needed. We also will have access to information through the PRP and clinic. We will make home visits to collect data on those who move out of the area. With these methods in ACHIEVE, we obtained 6 and18-month outcome data on 99% of participants.

7. DATA COLLECTION AND MEASUREMENTS

Outcomes and Measures are collected at baseline, 6, 12, 15 and 18 months at mental health programs**.** Table 2 shows these measures.

Primary Outcome: The primary outcome will be 7-day point prevalence smoking abstinence at 18 months, defined as self-report of 7 days of not smoking, confirmed by expired CO <8ppm with a Bedfont Smokerlyzer II .[175,181,182] Biochemical verification with available urine cotinine (if not on NRT) and/or anabasine will be used as needed to confirm self-reported abstinence, particularly if the validity of CO is expected to be low (e.g. COPD or difficulty forming an adequate seal on the smokerlyzer); and if CO is greater than 8 as this could be from second hand smoke or smoked cannabis. [148-150]

7-day smoking abstinence at 6,12 and 15 mo. are secondary outcomes.

Other Secondary outcomes focus on AHA metrics for health risk behaviors [165] and include: a) continuous abstinence with 1) % continually abstinent over 3mo. (based on self-reports of abstinence since last visit, using timeline follow-back)[183], and biochemical verification at 15 and 18 month visits), 2) total days abstinent in the study with the same method; b) Weight and BMI; c) Physical fitness with 6-minute walk;[184-186] and d) Healthy diet.[187] We will assess 10-year probability of a CVD event with the global Framingham Risk Score (FRS) incorporating smoking, total and HDL-cholesterol, systolic blood pressure and diabetes mellitus.[188] Others include: health status (SF-12)[189]; Quality of life (Euroqol);[190-192] psychiatric symptoms (BPRS);[193] ED use and hospitalizations.

We will also examine the difference of mean CO change over time between intervention arms, and, among

continuing cigarette smokers, change of mean number of cigarettes smoked per day over time between intervention arms.

Measurement methods: Measures for all participants are detailed below, and will be conducted using standardized procedures, and following quality control procedures as in ACHIEVE and Drs. Evins' trials. [51,61,121,125] The data collection team will be certified in and experienced with measures, and monitored by the study coordinator. All measures are collected at baseline, 6, and 18 months. At 12 months and 15 months we collect contact information, medications, smoking information, weight and event surveillance.

Demographics, Medical History: We will collect demographics, contact information, medical history with checklist of conditions, Rose Angina Questionnaire, and assess alcohol use with the AUDIT (Alcohol Use Disorders Identification Test) and questions from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-II) and substance use with ASI-Lite. [151,152]

Psychiatric diagnoses and medications are abstracted from charts. Participants confirm medications.

Tobacco smoking will be assessed with questions regarding self-reported smoking behavior since the last data collection visit and 6-item Fagerstrom Test of Nicotine Dependence (FTND). [147] At baseline we also assess smoking history including age of onset, cigarettes/day, pack-years, number of prior quit attempts, reasons for treatment failure or relapse, and self-efficacy around quitting. We will measure expired carbon monoxide (CO) and will also obtain urinary cotinine and anabasine as appropriate to confirm smoking status. [148,150,153]

Weight will be measured to the nearest 0.1 lb by a high quality digital scale with participants wearing light indoor clothes without shoes. Weight will be measured in lbs. for ease of interpretation by participants and converted to kg for calculation of BMI, calculated as the Quetelet index.

Height to the nearest 0.1 cm will be measured at baseline using a wall-mounted stadiometer.

Physical fitness will be measured by the 6-minute walk test, a valid predictor of VO2 max and responsive to increases in regular moderate physical activity. [154-156]

Blood pressure will be determined by the OMRON 907 XL, a validated device that records BP using an oscillometric technique. [157] On 3 visits, 1 week apart, 3 measurements (each separated by 30 seconds) will be obtained on the right arm of participants after they rest quietly in the seated position for at least 5 minutes. [158]

Fasting blood measures will be collected, centrifuged, aliquoted and sent for processing. Total and HDL cholesterol, triglycerides, glucose, LDL cholesterol will be estimated by Friedwald equation unless direct measurement is needed. [159] An aliquot will be frozen for future investigation of putative CVD risk markers. Urinary protein will be measured.

Waist circumference will be measured with anthropometric tape, in a plane 1 cm above the navel.

Questionnaires will be used for a variety of purposes including baseline descriptive data, outcomes to assess intervention effects, and mediators to assess potential causal pathways. Instruments may be added or removed depending on scientific and logistic considerations including participant burden.

Planned instruments are described here:

Healthy diet. Block Fat, Fruit, Vegetable and Fiber Screener Questionnaires provide self-report of daily fruit, vegetable intake, and percent energy from fat. [160] A sugar-sweetened beverage instrument will be used. [161] Health status will be measured by the Medical Outcomes Study SF-12. [162]

Quality of life will be assessed with the Euroqol EQ-5D, a brief 6-item instrument that is valid in persons with schizophrenia and bipolar disorder that can be used for cost-effectiveness analyses. [163-165] We will use the Neighborhood Questionnaire to assess participants' home environments for safe places to exercise and places to purchase healthy food, a questionnaire on food and shopping habits, and the Pittsburgh Sleep Quality Index. [166-168]

Medication adherence will be measured with an adapted questionnaire based on the Morisky Medication Adherence Scale for each class of medications for CVD risk factors (e.g., antihypertensives, lipid lowering medications). [169]

Psychiatric symptoms will be assessed by the Brief Psychiatric Rating Scale (BPRS). [170,171] Interviewers will receive training on administration and scoring and will rate 5 sample video administrations of the BPRS to ≥85% to gold standard ratings by consensus raters.

Self-reported physical activity will be measured with the Godin Leisure Time Exercise Questionnaire. [172]

Social Support will be assessed with the Medical Outcomes Study Social Support Questionnaire. [173,174]

To assess social networks around smoking, we will use the personal network approach measurement (also called the 'egocentric' approach) to elucidate the network ties that surround a focal individual. [175-179] In particular, we will ask each participant to identify the wide range of network members with whom individuals interact and measure the participant's understanding of the connections among those people. We will assess health literacy with the Health Literacy Skills Instrument. The sexual behaviors of persons with serious mental illness have implications for their emotional and physical well-being. These behaviors also affect the need for health care services that are focused on sexually transmitted diseases, family planning, and childbearing. Reproductive health will be measured with NHANES survey questions. [180] Health care access will be measured using adapted specific Behavioral Risk Factor Surveillance System Questions. [181] Access to technology will be measured using adapted questions based on PEW Research Center. [182]

Table 2. Data Collection Measures for All Participants	***BL***	***6***	***12***	***15***	***18***
Contact information	X	X	X	X	X
Demographics	X	X			X
Medical conditions	X	X			X
Substance Abuse	X	X	X	X	X
Medical history	X				X
Rose Angina	X				
Psychiatric diagnoses	X				
Medications	X	X	X	X	X
Physical measures					
Blood pressure	X	X			X
Weight	X	X	X	X	X
Height	X				
Waist circumference	X	X			X
6 minute fitness walk	X	X			X
Fasting blood measures	X				X
Urinary Cotinine and anabasine	X	X	X	X	X
Urinary Protein	X				X
Smokerlyzer CO	X	X	X	X	X
Instruments					
Healthy diet	X	X			X
Tobacco measures	X	X	X	X	X
Health status	X	X			X
Quality of Life	X	X			X
Neighborhood Questionnaire	X				X
Sleep habits	X				X
Medication Adherence	X	X	X	X	X
Psychiatric Symptoms	X	X			X
Physical Activity	X	X			X
Social Support					
Healthcare access questions	X				X
Technology	X				X
Reproductive health	X				X
Social Networks	X				X
Health Literacy	X				
Event Surveillance-safety	X	X	X	X	X

Event surveillance. We will identically apply a process to each randomized group and collect self-reported symptoms, health care utilization and records related to CVD and mental health outcomes, including ED use and hospitalizations, and use the SAFTEE[183] for possible medication side effects.

Intervention Measures: In active intervention participants, to measure interim progress towards goals, inform case management and analyze potential mediators: we will track 1) attendance at integrated groups, individual visits, exercise classes (staff report) and gym use (sign-in records), 2) self-reported smoking since last visit expired CO, 3) study medication use by self-report/interim pill counts, 4) weights from weigh-ins and text responses, and 5) texting use (% completed responses, smoking and eating behavior, weight, daily steps).

Interviews: We will use a purposive sample of active intervention participants, and we will conduct interviews after the 18-month intervention to gain an understanding of participant perceptions of and satisfaction with the program.

Organizational factors (Substudy of factors related to intervention implementation): To better understand factors influencing implementation of the intervention and potential future dissemination, we will conduct semi-structured interviews with selected community mental health program leadership and staff, psychiatrists and health coaches with involvement in the intervention, and targeted (N=50), and we also will survey more widely mental health staff and clinicians at mental health programs (N=150). Interviews will ask about the intervention's perceived effectiveness, ease, associated barriers, fit within the organization and financial models for continued support. We will discuss issues around physician prescribing of smoking cessation pharmacotherapy. We will interview before the intervention and then at end of study to assess changes due to the intervention. Surveys will focus on assessing implementation climate and attitudes towards evidenced-based practices, perceptions of the role of various sectors of the health care and social services system in addressing clients' somatic health needs; perceptions of the TRIUMPH intervention, its usefulness; barriers to implementation; stigma toward persons with SMI; and patient communication. We will gain an understanding of factors impacting intervention acceptability, feasibility and future sustainment, and prepare groundwork for dissemination. Study team members will conduct interviews in person and administer surveys using Qualtrics or paper.

Elements of RE-AIM framework: [184] We will collect data to report as many aspects of the trial as possible. For Reach, we will estimate the number of smokers and compare those eligible to those signing screening consent. We will also compare characteristics of those screened to those enrolled. For Efficacy /Effectiveness, we will report all our outcomes including potential adverse events. For Adoption, we will track pharmacotherapy prescription/use, attendance in all intervention contacts and use of text messaging, and report any site differences. For Implementation, we will track delivery of all intervention components, analyze cost (B3i5), and incorporate information from interviews about facilitators and barriers. For Maintenance, from interviews, we will explore plans for sustainment. We conceptualize this study as a Hybrid Type I trial testing a clinical intervention while gathering information on its delivery and its potential for future implementation. [185]

8. QUALITY ASSURANCE AND QUALITY CONTROL

Quality Assurance pertains to activities that promote collection of high quality data, and Quality Control refers to activities that detect emerging data issues with sufficient time to implement appropriate corrective actions. Our approach to Quality Assurance includes: 1) preparing a manual of operations; 2) implementing a master trainer model to train and certify other staff; 3) train and certify all data collectors; 4) recertify data collectors at least annually; 5) routinely calibrate equipment; 6) maintain logs of certified staff and calibrated equipment. Our approach to Quality Control includes: 1) monitoring counts of completed data collection items; 2) monitoring distribution of trial outcomes, overall, by data collector and site; 3) record lag time in data entry; 4) issue queries on missing data, out of range values or illogical data relations; 4) review types and distribution of data entry errors; and 5) prepare reports for staff, investigators and NIMH and DSMB on Quality Control.

9. RANDOMIZATION AND BLINDING

Randomization to intervention or control will be stratified by site and by whether participants are ready to set a quit date within 30 days or within 6 months. We aim to enroll approximately 60% of the participants in the strata for being ready to quit in 30 days. To prevent predictability of assignment, the randomization schedule will be created in variable block sizes. Prior to randomization, the study coordinator will confirm the participant meets all eligibility criteria and required baseline data are collected. Due to the nature of the intervention, participants and coaches will be aware of group assignment, however, we will take considerable efforts to ensure data collection staff will be kept blinded to assignment (e.g., exclude them from all parts of intervention delivery, remind participants not to share group assignment, designate/track unmasked staff).

10. INTERVENTION

Theoretical foundations and intervention framework The TRIUMPH intervention incorporates health behavior change techniques based on principles derived from cognitive and behavioral therapies and social

cognitive theory. [186-189,] Participants are placed in groups based on readiness to quit smoking as assessed by the Transtheoretical Model. [73-75] Motivational interviewing, a patient-centered and directive approach well suited to SMI, is used to enhance intrinsic motivation to stop smoking, increase exercise and improve diet. [190-193] The intervention is designed to be positive, goal-oriented and focused on identifying and overcoming each individual's specific barriers to behavior change. Importantly, the intervention conceptualizes tobacco dependence and obesity as chronic conditions, which require skill building and ongoing strategies to achieve and maintain healthy behaviors, consistent with a psychiatric rehabilitation and recovery model. [194,195]

Addressing weight and physical activity together with smoking cessation will exert a synergistic, positive effect on health outcomes. Working with participants to achieve healthy eating and exercise behaviors as a way to avoid weight gain may minimize this potential barrier to smoking cessation. Participating in group exercise can provide social support and serve as an alternate behavior to smoking. Moreover, exercise may alleviate some nicotine withdrawal symptoms (e.g., insomnia, negative affect) and have positive effects on abstinence. We also expect that smoking cessation will result in improved respiratory capacity and endurance, which will be evident during exercise sessions, and will provide positive, reinforcing feedback. We will base our examination of implementation issues on the RE-AIM framework[184].

Previous work has supported cognitive tailoring. [26,27,51,52,69,125,196] The intervention will be tailored to meet the cognitive needs of SMI who often have memory and executive function impairment. [197,198] Tailoring includes emphasized learning of specific and skills repeatedly, breaking material into small units, using learning aides to reduce memory and attention requirements, and rehearsing behavioral skills. [199-201] Materials emphasize message simplicity. Choices are limited to accommodate for decision-making deficits, e.g., coping strategies for smoking urges are distilled to the "4 Ds"—deep breathe, do something else, drink water or delay.

TRIUMPH Intervention goals focus on all 4 AHA CV health behaviors: smoking abstinence; healthy diet; healthy weight and regular physical activity. [202] The primary goal is smoking abstinence. Goals will be individualized weight goals based on baseline BMI (i.e., weight maintenance if normal BMI, weight loss if BMI ≥ 25) and provide intermediate weight, diet and exercise targets while maintaining a focus on smoking abstinence.

The TRIUMPH intervention is delivered separately from mental health or medical services the participants may already be receiving. The intervention is not a substitution for participants' ongoing mental health or medical care.

Intervention Components (Table 3)

Table 3. TRIUMPH Intervention Overview: Integrated Smoking Cessation, Weight Management and Exercise			
Phase	**Motivational Enhancement**	**Active Smoking Cessation**	**Relapse Prevention**
Inclusion	Interested in quitting, not ready to set date within 30 days*	Willing to set a quit date within 30 days*	2 consecutive weeks of smoking abstinence
Length	4 weeks (may be repeated up to 2x)	7 weeks (may be repeated up to 2x)	Ongoing until end of study
Intervention Components			
Group Sessions	-60 minutes weekly with coach -Focused on increasing motivation to quit and weight management -CO and weight monitoring	-60 minutes weekly with coach -Focused on setting and implementing quit date and weight management - Prior to the 1st smoking cessation group – prescriber to meet with participants to start medications (medications to start first week of group) -CO and weight monitoring	-60 minutes weekly month 1 -biweekly month 2, then monthly -Focused on relapse prevention and weight management -CO and weight monitoring
Individual sessions	20-30 minutes bi-weekly for 3 months, then monthly to review individualized goals (smoking and weight management) and support behavior change.		
Pharmacotherapy	Education, and participants may start pharmacotherapy with Varenicline (+/- NRT) or Bupropion + NRT	Varenicline (+/- NRT) or Bupropion + NRT	Varenicline (+/- NRT) or Bupropion + NRT
Exercise	Group exercise class, 50 minutes, 2-3 x/week Outpatient Ppts: DVDs, pedometers, group exercise classes		
Text messaging	Participants enrolled in text messaging campaigns based on Intervention Track and whether they have experience with text messaging.		
**Participants start the study in one of these phases, tailored to their motivation to quit*			

Table 4. TRIUMPH Intervention. Selected Examples of Strategies by Treatment Phase		
	Smoking Cessation Focus	Weight/Exercise Focus
Motivational Enhancement Phase		
Education	-Address knowledge deficits and correct misperceptions (e.g., fear of pharmacotherapy, "cold turkey" works)	-Address knowledge deficits and correct misperceptions about weight management (e.g., fear of weight gain after quitting)
Building success and motivation	-Build confidence by reducing smoking or making trial quit attempt; present peer models	-Discuss how experience of being more active in exercise class has influenced readiness to quit
Active Smoking Cessation Phase		
Self-monitoring	-Create awareness of smoking behavior -Identify smoking triggers -Track correspondence of CO with smoking behavior	-Create awareness of sugar sweetened beverage intake -Increase awareness of snacking habits and weight -Promote replacement behaviors like "get 200 steps not a smoke"
Coping with withdrawal and cravings	-Present coping strategies for withdrawal and craving	-Discuss low calorie, healthy choices to substitute for cigarettes (e.g., sugar-free lollipop or gum) -Discuss benefits of exercise on craving and depression
Preparing to quit	-Plan day of quit attempt including strategies to avoid triggers	-Plan what food to have available on quit attempt day. -Plan exercise schedule for week of quit date for less idle time.
Relapse Prevention Phase		
Coping with stress	-Broaden coping strategies for stress	-Advise crunchy fruit and vegetables not junk food when stressed -Exercise as a way to reduce stress.
Rewarding yourself	-Identify and implement rewards other than smoking	- Identify non food rewards for meeting goals -Focus on personal identified benefits of weight loss and fitness
All phases		
Social support	-Facilitate participation in a group with others who are working to attain similar goals -Supportive text messages	-Provide additional smoke free environments and activities (e.g., group exercise, gym) -Encourage support among group for healthier food choices

Integrated Smoking Cessation and Weight Management Group sessions. Participants will enter a group tailored for their readiness to set a smoking cessation date. Participants will move sequentially from one type of group to the next, from motivational enhancement to smoking cessation as they progress to being ready to quit within 30 days, and then to relapse prevention when they attain abstinence. Participants who do not progress may repeat group curricula as needed. We have previously used all the group curricular elements successfully. Drs. have found structured groups to be highly successful in contributing to attaining and maintaining smoking abstinence. [26,27,51,52,67,69] Similarly, we have found groups to be powerful in creating a supportive environment for weight management and exercise in SMI. [122,125]. Groups will include time for individual weigh-ins and include instruction in using medications including NRT.

Motivational enhancement phase**:** Participants not ready to set quit date within 30 days at baseline enter this group. Content will focus on improving perception of feasibility and benefits of attempting to quit smoking. Videotaped interviews with previous patients will illustrate increased readiness to make a quit attempt among peer models. Care will be taken to understand specific concerns about quitting smoking (e.g., fear of weight gain, symptom exacerbation), to problem-solve barriers and envision each participant's cessation strategy. We will educate participants about pharmacotherapy, and participants may initiate pharmacotherapy. We will encourage exercise as a strategy for improving readiness and ability to quit. The goal of this phase is to explore and resolve ambivalence regarding quitting, move to being ready to set a quit date within 30 days, and

enter the 7-week active smoking cessation group. Those not ready will repeat the motivational enhancement group. If they are still not ready to set a quit date after the 2nd course, they will work with their coach in individual visits to explore barriers and reasons to quit with the goal of increasing motivation to join an active smoking cessation group.

Active smoking cessation phase includes participants expressing readiness to try to quit smoking within 30 days. The group will prepare for their quit date, set between weeks 4/5, and pharmacotherapy is initiated in this phase. Expired carbon monoxide (CO) will be measured weekly. Participants will self-monitor smoking triggers and develop plans for how to handle triggers after quitting. Skills training will enhance coping with urges to smoke, physical withdrawal, and psychiatric symptoms. (Tables 3/4,) Videos of peers and peer guest speakers will be included to increase self-efficacy through identification with a successful peer model. Smoking issues specific to those with SMI will be discussed. Eating, exercise and weight management strategies will be incorporated throughout, paralleling smoking-related content. This group may be repeated.

Relapse prevention phase. Participants join this phase when they achieve ≥14 days biochemically confirmed continuous abstinence at the end of the 7-week smoking cessation phase. Sessions focus on learning and applying key cognitive and behavioral skills to high-risk situations, including refusal skills, problem-solving, identifying and responding to permission-giving beliefs, and developing and implementing personalized relapse prevention plans. Weight management strategies for high-risk situations and problem solving will be integrated throughout. (Tables 3, 4). Those who slip or resume smoking will be asked to remain in the group with the goal of regaining abstinence through subsequent supported quit attempts.

Individual sessions with the health coach will focus on reviewing progress and problem solving to enhance participants' strategies for smoking cessation and weight management. The coach will review relevant process data tailored to individuals' needs (e.g., expired CO, study session participation, gym use, use of texting, medication adherence, expired CO, weight, and step counts), and using motivational interviewing, will provide feedback and address readiness to adopt further changes. The potential synergistic effects of efforts to achieve goals across more than one type of health behavior will be discussed and reinforced as appropriate. Additional sessions may be scheduled for those not ready to set a quit date after 2 cycles of the 4-week motivational enhancement program or for those who do not achieve 2-week abstinence after 2 7-week active smoking cessation cycles. These participants will continue to participate in all other aspects of the intervention, and will be reassessed and encouraged to rejoin the appropriate group when ready.

Pharmacotherapy for smoking cessation in SMI is universally recommended, but infrequently used in most settings. [12,72] The study physician(s) are trained education on use, risks, benefits and monitoring of pharmacotherapeutic cessation aids in SMI, and will prescribe and monitor medications for intervention participants, coordinating with and supported by others on the study team. These psychiatrists will discuss medication choice with participants and take their preferences into account while assessing clinical appropriateness for varenicline+/-NRT, and bupropion+NRT (patches with lozenges/gum) Varenicline has been associated with higher abstinence, [67,203,204] so we expect it will be used preferentially. We will use standard dosing for varenicline and buproprion. Varenicline dosing is 0.5mg for 3 days, 0.5 mg bid for 4 days and then 1mg bid. Subsequent prescriptions are 1mg po bid. Varenicline will be provided by Pfizer. Bupoprion is 150mg pod bid SR formulation. Those with adverse effects with varenicline limiting tolerability will be offered a lower dose, or bupropion+NRT. Bupropion+NRT will be offered to those with varenicline contraindications, and vice versa. Once initiated, the goal will be for participants to use medication for the study duration for sustained abstinence, however, if needed they may stop and then resume medication or switch therapies. This flexible approach should improve cessation rates. Physician study visits for smoking cessation pharmacotherapy are separate from the participants' regular mental health visits. Participants will continue to see their regular psychiatrist for mental health care. The physicians prescribing smoking cessation pharmacotherapy will be study team members and will communicate with the participants' regular psychiatrists about the intervention, but will not deliver regular mental health care.

Exercise program. Three approaches will enable participants to achieve 150 mins/week of moderate intensity

physical activity.[205] First, group exercise classes will be held two to three times a week at mental health programs. Under supervision of the intervention director, exercise leaders will deliver classes following a progression appropriate for sedentary adults and designed to build exercise confidence.[206] Second, participants will be provided access to a local gym (e.g., at Bayview, or City of Gaithersburg's Bohrer Park gym facilities). Participants will be provided with 3 orientation sessions teaching them to use the aerobic fitness equipment (e.g., treadmills, stationary bicycles). Third, we will use text messaging prompts and pedometers to encourage participants to achieve a 10,000 steps per day goal[207]. Exercise instruction will be adapted to the heterogeneity of this population including psychiatric symptoms, motor control challenges and cognitive levels.[121,122,124,125] During individual sessions, coaches will help participants develop individualized physical activity goals and strategies to overcome related barriers (e.g., preparation for class, places to walk). Exercise videos will be distributed.

Text messaging support. Texts will provide reminders to use behavioral strategies introduced in group and individual sessions, will encourage self-monitoring (e.g., weight, pedometer steps, number of cigarettes) and provide positive feedback for attainment of targeted goals, tailored to the participant's intervention phase. For example, in motivational enhancement, messages will focus on personal benefits of abstinence and preparing for a trial quit date; in active smoking cessation, texts will count down to the quit date and remind participants to use pharmacotherapy. Eating and exercise messages will parallel and integrate with smoking-related content (Table 4) (e.g., choosing healthy foods and exercise to cope with stress). Responses are captured in a database enabling the coach to track and review participant progress, thereby creating accountability and connection to the coach between intervention sessions. Participants will be provided cell phones and/or offered a prepaid phone card if they do not have phones/unlimited texting, allowing for connection to the platform and to other participants. Participants will be oriented to the texting platform. Smoking messages will be based on NCI's Quitnowtxt.[208] Text messaging support will be piloted and interviews will be conducted with smokers with SMI to assure ease of use, acceptability and satisfaction with the technology.

Self-monitoring: Participants will be encouraged to track eating, weight, exercise and smoking behaviors appropriate for their individually tailored behavioral goals and cognitive abilities using texting, and paper trackers if needed Coaches review data with participants at individual sessions and with the intervention team in case management.

Reinforcements: Contingency management reduces smoking in those with SMI and has been used by the team.[209-211] [148,149] and for attending 2 exercise groups/ week. Reinforcement plans are small incentives for group and individual session attendance and for low smokelyzer or cotinine readings. These will consist of earning points that may be traded in for small gifts, or earning up to $3 for session attendance or biochemically confirmed smoking abstinence with low smokelyzer reading or cotinine value.

Peer mentor guest speakers. In addition to the videotaped peer presentations, trained peer mentors from Dr. Dickerson's smoking cessation studies will be invited as guest role models in selected group sessions to provide encouragement and increase self-efficacy for smoking cessation. They are trained and will provide short testimonials focused on their experience of mental illness, smoking history and successful abstinence.

Health coaches leading the integrated sessions will be community mental health program employees. Embedding coaches at sites will enable optimal coordination of intervention implementation and allow them the opportunity to take advantage of everyday encounters, in addition to scheduled sessions, to reinforce healthy choices and behavior change (e.g., encouraging exercise participation). Coaches will have a background in mental health and/or health behavior change with a skill level typical for a community health educator, and will not require a Master's degree.[212] The coach is modeled after a position that would be feasible and sustainable in a community mental health setting. Coaches will receive training in all aspects of the TRIUMPH intervention and have supervision and ongoing interaction the Intervention Director and investigators.[213,214]

Training, case management and quality control: High-quality intervention delivery will be assured by providing initial and ongoing training of manualized approaches to smoking, weight management and exercise. Coaches

will receive intensive baseline training in motivational interviewing, group facilitation and conducting individual sessions for health behavior change in SMI and will attend Tobacco Treatment Specialist training.[215] They will follow Leaders' Guides and session outlines; exercise leaders will follow a standard protocol. Case management will be provided through regular meetings between coaches and supervisors. Quality control will be assured through reviewing a sample of group and individual sessions, taped or observed in person, rated for fidelity. Feedback will be shared with coaches.

11. CONTROL GROUP

Those assigned to the control group will receive usual care and will also receive referral to a telephone smoking quit line, a list of exercise resources and the NHLBI brochure Aim for a Healthy Weight. They will also receive a quarterly health newsletter.

12. DATA MANAGEMENT

We will store data in REDCap.[216] Built-in range and logic checks will prompt data checks and confirmation in real-time during data collection. The analyst will routinely conduct thorough checking and cleaning, examining distributions and data patterns and evaluation to detect inconsistencies. Outliers (e.g., extreme weight changes) will be identified using Rosner's extreme Studentized deviate (ESD).[217] Every effort will be made to determine correctness of outliers in a timely manner. Confirmed outliers will be flagged and set aside in the principal secondary analyses. Those removed will be treated as all other missing data; sensitivity analyses will be conducted to assess influence of outliers on results. The analyst will create detailed variable documentation and conduct analysis per protocol under direction of Dr. Wang, statistician.

13. DATA ANALYSIS

Primary Outcome: The primary outcome will be 7-day point prevalence smoking abstinence at 18 months, defined as self-report of 7 days of not smoking, confirmed by expired CO <8ppm with a Bedfont Smokerlyzer II.[148,153,218] [182] Biochemical verification with available urine cotinine (if not on NRT) and/or anabasine will be used as needed to verify self-reported abstinence, particularly if the validity of CO is expected to be low (e.g. COPD or difficulty forming an adequate seal on the smokerlyzer); and if CO is greater than 8 as this could be from second hand smoke or smoked cannabis.[148-150]

7-day smoking abstinence at 6,12 and 15 mo. are secondary outcomes.

Other Secondary outcomes focus on AHA metrics for health risk behaviors[202] and include: a) continuous abstinence with 1) % continually abstinent over 3 mo. (based on self-reports of abstinence since last visit, using timeline follow-back[219],and biochemical verification at 15 and 18 month visits), 2) total days abstinent in the study with the same method, b) Weight and BMI; c) Physical fitness with 6-minute walk;[154-156] and d) Healthy diet.[160] We will assess 10-year probability of a CVD event with the global Framingham Risk Score (FRS) incorporating smoking, total and HDL-cholesterol, systolic blood pressure and diabetes mellitus.[220] Others include: health status (SF-12)[162]; Quality of life (Euroqol);[163-165] psychiatric symptoms (BPRS);[170] ED use and hospitalizations.

We will also examine the difference of mean CO change over time between intervention arms, and, among continuing cigarette smokers, change of mean number of cigarettes smoked per day over time between intervention arms.

For the primary outcome, we will also perform sensitivity analyses using expired CO<6ppm for abstinent confirmation, as this cutpoint has become more acceptable during the time the trial has been implemented.[150] The outcome using this alternative definition will be modeled in the same fashion.

Our recruitment goal is 220 participants will be recruited from 2 community mental health organizations, enrolled, and randomized in equal allocation to active intervention (Group B) and control (Group A), stratified

by site and by willingness to set a quit date within 30 days. The enrollment goal is 50% willing to quit in 30 days. Formal assessments are at baseline, 6, 12, 15 and 18 months. Primary analyses will utilize smoking cessation evaluations at 6,12, 15 and 18 mo. and be conducted under the intention to treat principle.[221] The primary outcome is at 18 mo.

Core analytic model**:** GEE based logistic regression modeling will be conducted using SAS Proc Genmod (or the Stata or R-equivalents) with a logit link and a within-individual, unstructured working correlation model. The primary outcome of smoking cessation at 18 months will be modeled together with the secondary outcomes of smoking cessation at 6,12 and 15 months.
Let Y_{ijk} denote the binary primary outcome of smoking cessation for the i^{th} participant at the j^{th} visit (j = 1, 2, or 3), corresponding to the 6-, 12- and 18-month visits), in the k^{th} treatment group (k = 0 or 1 corresponding to intervention groups A and B). X_{ik} is a vector of pre-randomization covariates (which will include study site indicators). The mean model for the longitudinal data structure of the primary analysis is:

$$\text{logit}\{E(Y_{ijk})\} = \text{logit}\{P_{jk}\} = X_{ik}\eta + \alpha_j + \beta_j \times k \quad (1)$$

so that β_3 represents the adjusted log odds ratio of smoking cessation rate in the intervention vs. the control group at the 18-month visit. Although this mean model could be implemented though a random effects (mixed effects) model in GlimMix, the population-level interpretation of the estimated odds ratios changes with the magnitude of the random effect. For ease of interpretation, we will estimate our primary mean model through the GEE approach in GenMod with resultant estimates representing population average odds ratios.

Although model (1) will support our principal analyses, there is an attractive, transition model alternative. A first-order, autoregressive transition model is a useful adjunct to (1). Note for each participant the outcome is a binary time series that can be analyzed via a series of linked, 2×2 tables (rows are values at visit (j-1), columns at visit j, where visit 0 is baseline), with transitions modeled by logistic regression with treatment effects and, if desired, other covariates. This model could be used to characterize probability of successful abstinence at 12-months among those who were still smokers at 6-months, and at 18-months among those who were smokers at 12-months. Similarly we could estimate relapse rate at a given visit among quitters at the previous visit.

Missing data: Based on our experience, we anticipate less than 10% of follow-up data will be missing.[125] Prevention is far superior to statistical treatments; every effort will be made to collect data on all randomized. We will use two approaches to missing data. First, in smoking cessation trials, conventionally, those missing smoking data are assumed to be smoking, and we will use this method to be comparable to the field.[203,204,222,223] Second, we will perform analyses on the assumption that data is missing at random (MAR). The underlying missing data process determines the biasing effects of missing data and structures valid analytic strategies.[224] If the probability of a potential observation being missing depends on what has, but not on what has not been observed, termed MAR, then estimates based on an appropriate analytic model (both the mean and error structure) for the observed data will not be biased. A valid model for the observed data allows the missing data process to be ignored. If missing is informative, meaning that the probability of an observation being missing depends on the value of that observation after accounting for all the observed data, then bias cannot be avoided by modeling the observed data alone, and the impact should be evaluated using sensitivity analysis. Given that MAR is not a testable hypothesis, we will perform sensitivity analyses to evaluate the robustness of MAR results with multiple imputation using a model derived from our analytical model under MAR, maintaining the covariance structure and modifying the imputation mean according to informative missing data scenarios.

Secondary Analyses (Secondary Aims 1-2): The odds ratio of maintaining continuous abstinence over 15 to 18 months months will be modeled using logistic regression. To evaluate between group difference in change for secondary continuous outcomes such as continuous smoking abstinence (number of days abstinent), weight, 6-minute walk test, global FRS, and psychiatric symptoms (BPRS), we will use linear mixed models employing visit by intervention interaction terms in the mean model and unstructured correlation in the covariance model to estimate intervention effects over time. Outcomes will be log-transformed as appropriate. Emergency department visits and hospitalizations over the three 6-month periods (0-6, 6-12, 12-18 months) will be modeled using mixed effect Poisson regression. All these analyses will be conducted under intention to treat principles. Covariates such as study site and set quit date indicators and other variables associated with

presence of missing data will be included in the mean model as appropriate.

We will also explore the difference of mean CO change over time between intervention arms, and, among continuing cigarette smokers, change of mean number of cigarettes smoked per day over time between intervention arms using mixed effects regression modeling approach in a similar fashion. For the first exploratory analysis, we will use all patients in the analysis. In the second analysis, we will determine if patients who continue to smoke, smoke less. In this analysis, we will include only patients who are not abstinent. We will use the pattern mixture approach by examining patients in separate groups according to their pattern of missing data to better understand the probability of missing based on patterns of the observed data to inform proper modeling and sensitivity analyses addressing potential informative missing mechanism.

Exploratory Analyses: (Aim 3) We will explore for the potential of treatment effect differential between the participants who are ready to set a quit date within 30 days at baseline and those who are not. This analysis will be conducted under the intention to treat principle and will involve stratified analysis or statistical modeling invoking an interaction term between the status of setting the quit date and the parameter capturing the intervention effect. The trial is not powered to detect such an interaction but the result should be informative for future intervention and trial design. For other subgroups of interest defined at baseline (e.g., psychiatric diagnosis), we will adopt a similar analytic approach. In addition to analyses that preserve the intention to treat principle, we will perform informative exploratory analyses based on subgroups defined post-randomization to characterize aspects of the intervention that may be related to improved abstinence, weight, fitness and psychiatric outcomes in the active group. Such analyses will use post-randomization variables that are potential mediators –e.g., group and individual session visit and exercise class participation, specific pharmacotherapy use and adherence, and text-message self-monitoring activities. [225] Even so, these analyses are more prone to biases because protection from confounding afforded by randomization is not likely applicable. Propensity score stratifications will be used to manage potential confounding in these analyses. Nevertheless, these findings will be interpreted with caution and will be considered exploratory.

Cost Analysis (Aim 4) will be conducted primarily from an adopting organization or payer's perspective (e.g., Medicaid) estimating incremental intervention implementation costs relative to control. Resource measurement will focus on sampling and tracking intervention staff time. We will sample at specified intervals for 1 week at a time. Tracking specific tasks will allow us to eliminate time spent strictly on research and perform sensitivity analyses with different potential levels of efficiency (e.g., amount of active client involvement vs. administrative time). We will use medication data and data on MD visits and hospitalizations to calculate cost per participant and total costs. With estimates of total costs, we will estimate incremental intervention costs and incremental costs per incremental improvement in 1° and 2° outcomes. To extend the time horizon forward, we will use the global FRS to project the proportion expected to have a CV event within 10 years and the present value of costs and QALYs associated with events, allowing us to perform a societal perspective cost-utility analysis. [226] For all analyses, we will conduct univariate sensitivity analyses by varying assumptions and assess estimate uncertainty by bootstrapping for 10000 replications, drawing samples with replacement where samples have the same number of observations as the main study. [227]

Qualitative Analysis (Aims 5-6): Interviews will be transcribed and coded. NVivo will be used to enter and group discrete passages from data into themes. We will use the constant comparative method[228] to categorize transcript statements that demonstrate common attributes, then combine categories into broader, recurrent themes using a hybrid approach where we will start with larger categories and then add nodes and subnodes as new concepts emerge until saturation of ideas is reached. Findings will be shared with study sites and the Advisory Committee to inform ongoing implementation and future sustainability and dissemination.

Power analyses: Under a conservative set of assumptions, this trial with sample size of 220 will have ≥80% power to detect a clinically meaningful effect in our primary outcome of 7-day point prevalence smoking abstinence at 18 months between intervention and control (Table 5). We assume:
1. Two-sided alpha =0.05.
2. Follow-up for primary outcome=100%. In smoking cessation trials, those lost to follow-up are classified as

smokers.[203,204,222,223] (B3i2).

3. Control group smoking abstinence rates of 3-5%. In RCTs of smokers with schizophrenia motivated to quit, those assigned to placebo + behavioral treatment have quit rates of only 4-5% at 12 weeks.[24] No behavioral treatment other than quitline referral is being offered to controls in this study. The estimate acknowledges controls' interest in quitting and the possibility of receiving pharmacotherapy outside the study.

4. Active group abstinence rates of 17.5 - 21.5%. We present the combined overall estimated range of abstinence rates (Table 5, row C) as an average of those in the 2 strata, 1) initially willing to set a quit date in 30 days (row A) and 2) those not initially ready to set a quit date within 30 days (but willing in 6 months) (row B). Row A shows for those ready to set a quit date within 30 days, we project abstinence rates of 25-30% consistent with the 28% 14-day point-prevalence abstinence rate at 12 months we found with varenicline and group behavioral therapy (B1e).[67] The rates are also consistent with 32% abstinence in a trial 12 weeks after discontinuing 12-weeks of bupropion, NRT+ behavioral therapy.[51] This is somewhat higher than 21% abstinence reported in 12-week RCTs of varenicline in schizophrenia,[24,30,60] reflecting higher abstinence rates we achieved when combining varenicline[67] and other medications[26,51] with intensive, structured group therapy.

Table 5. Statistical Power to Detect Differences for Smoking Abstinence by Percent Abstinent in Control and Intervention Groups

Ranges of abstinence rates in active intervention group					
Willing to set quit date within 30 days* (A)	25%	26%	27-28%	28-30%	30%
Not initially ready to set quit date within 30 days* (B)	10%	10%	10-11%	10-12%	12%
Overall % abstinent in active intervention group (C)	**19%**	**19.6 %**	**19%**	**20%**	**21%**
Overall % abstinent in Control group	Statistical Power				
5%	.80	.83	.87	.91	.94
4%	.89	.90	.93	.95	.97
3%	.94	.96	.97	.98	.99
With 50% of intervention group in A and 50% in B, C is average of A+B					

For participants initially not ready to quit within 30 days (B), we conservatively project abstinence of 10-12% based on results of 42% moved to "action" after 4-week motivational enhancement,[89] and applying that percentage to estimates of abstinence rates in those ready to set a quit date in 30 days (A). Abstinence rates for those not initially ready to quit (B) could actually be > 12% due to social support and modeling in exercise groups, as those initially not ready to quit in 30 days exercise together with those willing to quit in 30 days.

We realize trials of 18-month comprehensive smoking cessation in SMI have not been published; nonetheless we believe that our design, building in repeated cycles of groups combined with individual visits, text support and exercise provides strong rationale for the projected abstinence rates. We will have sufficient power to detect a highly clinically relevant treatment effect even under scenarios where the active group would have lower overall quit rates than our experience would support. Thus, we believe the estimated abstinence range is well justified.

We also have precision for estimating clinically significant intervention effects in secondary outcomes. The 95% confidence interval (CI) for an effect estimate is +/-1.96* sqrt(2/n)*σ, where n is the sample size per group and σ the common SD for change in the measured outcome of interest for both groups. The precision for the mean estimate of the intervention effect of difference in mean change between groups would be: weight 5.0 lbs; six minute walk 50 feet and 1.2% for the minimal detectable overall reduction in global FRS.

14. DATA SECURITY

Each participant will be assigned a study ID number that will be used, instead of name or other identifying information, on all study data collection materials. The link between identifying information and the study ID will be kept in a separate database with password access available only to the data analyst and principal investigators. Paper records will be kept in locked file cabinets. Data will be published only in aggregate, with no identifying characteristics of individuals published or presented. All study staff annually sign a confidentiality statement attesting to their understanding of, and willingness to abide by, written policies on research ethics and confidentiality. For data entry and management, we will use REDCap, a web-based application for building and managing data entry and databases.[216] REDCap data is housed on secure servers at the Johns Hopkins Biostatistics Center under firewall protection with offsite access through VPN. The database will contain

embedded checks for internal consistency and data completeness. Missing and questionable data will be queried in source documents and corrected, and double data entry will be performed for primary outcome data. Database access is password protected and restricted to authorized personnel only (e.g., data collectors cannot see intervention data), and REDCap provides audit trails for tracking data manipulation and user activity. Data will be exported from REDCap to SAS for analysis. Analytic files will be stored on secure Johns Hopkins network servers and accessed on encrypted and password-protected computers.

15. HUMAN SUBJECTS.

All study staff will complete the web-based Collaborative Institutional Training Initiative (CITI) for Basic Human Subjects Research, Conflict of Interest Training and training in the Health Insurance Portability and Accountability Act (HIPAA).

Study participants will be 220 adults, aged 18 and older with nicotine dependence who attend psychiatric day programs or outpatient mental health clinics affiliated with Johns Hopkins Bayview or Family Services Agency, Inc. All participants in the trial provide written informed consent using procedures reviewed and approved by Johns Hopkins Institutional Review Boards. There are separate consents for the screening and intervention phases of the study. The consent forms cover all procedures done as part of screening and the intervention.

Sources of materials

Sources of materials: Data collectors will conduct assessments in-person; their regular presence on-site during data collection periods will minimize participant burden and allow measures to be performed according participants' schedules and availability. Eligibility will be determined through in-person screening at the study sites. To determine eligibility for the study, we will obtain permission from potential subjects to talk with mental health program staff and clinicians and contact their primary care physician and psychiatrist concerning any medical or psychiatric reasons for study exclusion. We will communicate with these physicians to ensure there are no contraindications to participating in the intervention. [229] We will document assessments and in each subject's study chart. We will also communicate this information to participants and ask participants for permission to communicate this information to their medical and psychiatric providers.

Safety Monitoring

Participant safety will be closely monitored. Protection of research participants begins with the eligibility criteria, which are designed to exclude individuals with a serious medical condition or psychiatric instability that would make it unsafe for them to take part in the smoking cessation, weight maintenance and exercise intervention. During the study, regular mental health and primary care will be provided by the participant's usual mental health and primary care providers, not by the study. Participants will be made aware of this delineation of responsibility.

We will carefully monitor the safety of enrolled participants. If a participant develops a medical or psychiatric issue, the safety of continuing or resuming the intervention will be ascertained by the study clinician in collaboration with the participant's regular providers. Surveillance for serious adverse events and other relevant clinical events will occur by questionnaire at regularly scheduled intervals.

We may be come aware of medical problems including abnormal blood pressure or laboratory tests. Results of routine clinical labs and physical measures obtained as a part of data collection will be provided to participants and physicians at baseline and after study completion. Measures meeting criteria for alert values will be communicated more quickly as described below.

A study clinician (safety officer) with appropriate expertise will be responsible for reviewing medical eligibility criteria, clinical measures and laboratory values and will be the primary contact for staff, participants and physicians for medical issues. This clinician will review and report any serious adverse events and will have appropriate coverage during absences to provide 24/7 medical safety coverage for the study.

16. POTENTIAL RISKS

Summary of Potential risks: The study assesses the effectiveness of the combination of evidence-based smoking cessation, weight management and physical activity interventions for adults with SMI. Recommended treatments, both behavioral/lifestyle and pharmacologic, are based on national guidelines. [202,230] Sources of risk include medication-related adverse events, such as nausea, abnormal dreams, or insomnia from pharmacologic smoking cessation aids. Behavioral interventions and improved health behaviors from the intervention (e.g., weight loss, physical activity) infrequently may lead to hypoglycemia or hypotension, particularly in those taking oral hypoglycemic or antihypertensive medications and necessitate adjusting diabetes or blood pressure medications. Physical activity is associated with a small risk of cardiovascular complications (less than 1 per 187,500 person-hours of exercise). [229] Physical activity can also increase the risk of musculoskeletal discomfort or injury. [231] Phlebotomy causes minor discomfort and can cause bruising at the venipuncture site. Many participants who quit smoking will experience transient nicotine withdrawal symptoms and are at risk for weight gain. Loss of confidentiality is also a risk of participation.

Potential Risks

A. Study Medication

1. Nicotine Replacement Therapy (NRT). Among the approximately 4,000 compounds in tobacco smoke are carcinogens such as nitrosamines, irritants such as a variety of phenolic compounds, volatiles such as carbon monoxide, and of course nicotine. The goal of this study is to reduce the morbidity and mortality of cardiovascular disease in a population with very high rates of nicotine dependence. The proposed method is via long-term treatment with pharmacotherapy and cognitive behavioral therapy to aid sustained tobacco abstinence and diet and exercise to minimize weight gain and further improve cardiovascular health. The proposed pharmacotherapy intervention is up to 18 months, and may include nicotine replacement therapy at doses of up to 39 mg per day. [51]

NRT is a powerful aid to smoking cessation with well-established efficacy. [232-235] Safety of NRT in patients with SMI has been established in several small studies. One important trial examined the effects of a 21 mg nicotine patch on smoking behavior, nicotine levels in blood and signs of toxicity in patients with schizophrenia. [236] In this crossover trial, 10 male veterans were monitored while wearing nicotine vs. placebo patches. The nicotine patch condition was associated with increased nicotine levels without signs of toxicity and decreased CO levels in 80% of patients. And in double blind, placebo controlled trials of bupropion added to nicotine patch alone [28] and with nicotine patch + nicotine gum or lozenge [51] the treatment was effective and well tolerated. NRT is now recommended to be given with bupropion as part of the PORT clinical practice guidelines. [56] Growing evidence shows NRT is safe and efficacious when used with varenciline. [237]

Safety of the nicotine patch, gum and lozenge have been well established. The risks of use of nicotine-containing medications are considered to be far less than those associated with tobacco use. [238,239] The nicotine patch is a transdermal therapeutic system that releases nicotine for 18-24 hours to reduce symptoms of nicotine withdrawal. Nicotine gum and lozenges provide short, rapidly acting nicotine in 2 or 4mg doses. The main adverse effect of nicotine in tobacco products is addiction, which sustains tobacco use. Because the study participants are nicotine-dependent, they will substitute nicotine from tobacco smoke for nicotine from a transdermal patch. Tobacco smoke constituents other than nicotine are responsible for the adverse health effects of smoking. The benefit of NRT outweighs the risks, even in smokers with cardiovascular disease. Carcinogenic nicotine-derived nitrosamines may be formed in the body under certain conditions after administration of nicotine medications, but switching from tobacco smoking to nicotine patches significantly reduces nitrosamine levels. [240] Nicotine is a potential fetal teratogen and may contribute to obstetric complications in pregnant women and to sudden infant death syndrome. While NRT during pregnancy is potentially hazardous, it is likely to be less hazardous than cigarette smoking, which exposes both the mother and fetus to both nicotine and a myriad of other toxins. Nonetheless, pregnant women will be excluded from the study and referred for individualized smoking cessation and prenatal care.

Smoking is associated with insulin resistance and hyperinsulinemia and long-term use of NRT may also be associated with insulin resistance.[241] Nicotine is associated with angiogenesis in several settings: in vitro models of ischemia.[242] improved wound healing in diabetes models[243] and growth of tumor and atheroma.[244] These effects are mediated by nicotinic receptor activation in endothelial cells; and through inflammatory processes.[245] Second hand smoke is believed to cause lung cancer, an effect mediated in part via nicotinic acetylcholine receptors.[246] Nicotine replacement products have low abuse liability compared to tobacco products, but the liability may not be equal across all medications. Abuse liability is likely to be greater with those products that deliver nicotine rapidly. The prevalence of abuse (i.e., use for reasons other than smoking cessation) and of dependence (i.e., difficulty stopping) with currently available nicotine medications is nil (nicotine patch) or very low (<10% of users of nicotine gum, nasal spray, inhaler). Motivated subjects can stop long-term nicotine gum use without relapse to gum use or smoking by either abrupt cessation or brief tapering.[247] Even if dependence to NRT develops, there is likely to be an overall health benefit if the individual is no longer smoking tobacco. NRT is thought to have vastly fewer adverse health consequences compared with smoking and has been shown to be safe for use in humans. If longer-term use of NRT is associated with reduced smoking, the health effects are expected to be beneficial compared to smoking.

Is it safe to give over 21-22 mg nicotine? Transdermal nicotine relieves nicotine withdrawal and doubles smoking cessation rates, and the high dose, 21 and 22 mg nicotine patches produce a steady state serum nicotine level that is often less than that obtained from smoking. In 63% of smokers of >20 cigarettes per day, a 4-week trial of 44 mg nicotine patches produced cotinine levels lower than baseline levels.[248] Participants in our prior smoking cessation studies smoked an average of 27 cigarettes per day at enrollment. Because the 21 mg patch is recommended for patients who smoke 20 cigarettes per day and smokers with schizophrenia extract more nicotine per cigarette than those without schizophrenia, a single 21 mg patch per day would provide substantially less nicotine per day than most patients with schizophrenia obtain from cigarette smoking. We propose to allow participants to use NRT patches and flexibly titrate their nicotine dose with additional short acting NRT in the form of NRT gum or lozenges to be used up to 18 mg per day as in Evins et al 2007. Therefore, although participants will obtain up to 39-40 mg nicotine per day, we may well be under-dosing participants. For heavy smokers, high dose nicotine patch therapy, 44mg/day, provides a higher percentage of cotinine replacement and better relief from withdrawal symptoms than 22 mg patch. In one study there was a significant association between higher patch dose and abstinence rate while using the higher dose patch but not after discontinuation.[249] Conclusions were that 44 mg NRT per day is safe for use in heavy smokers, that withdrawal symptom relief can be improved with more complete nicotine replacement and achieving a greater percentage of nicotine replacement may increase the efficacy of NRT. In people smoking >30 cigarettes per day there was a linear relationship between dose of nicotine patch (0, 21, 35, and 42 mg/day) and cessation rate and the rates of dropout due to side effects was not related to dose.[250] The authors suggested that longer durations of treatment may be necessary to show greater advantages from higher doses. In a comparison of NRT patch 22 mg vs 44 mg per day, those on 44mg per day achieved higher abstinence rates (68% vs 45%, $p<0.01$) prior to NRT taper.[251] This difference did not persist after tapering off NRT. Smokers with lower baseline serum nicotine and cotinine levels had greater success with smoking cessation with a 21 mg patch.[252]

What are the health risks of 18 months of NRT? Nicotine patch, gum and lozenges are available over the counter, without physician oversight. The manufacturers recommend that they be tapered after a 3-4 month trial. However, NRT is often used for longer, and risks are minimal. After a placebo-controlled trial of nicotine gum in 315 patients, 46% of abstinent smokers used nicotine gum beyond the recommended 4-month period. Ten months after cessation 17% of quitters were still using NRT gum. Gradual reduction of nicotine gum did not result in withdrawal.[253] In another study, 6% of participants in a 3-month smoking cessation trial reported use of nicotine gum at a 6-month follow-up assessment, and 67% of persistent users reported they were using gum to establish or maintain abstinence. An analysis of purchase pattern in the US provides similar estimate of extended use of NRT. In a national panel of 40,000 US households, 2690 recorded NRT purchases. Among 805 households that purchased nicotine gum, 6.7% of new purchase incidents led to monthly purchase of gum for ≥ 6 months.[254,255] Health Canada states on its web site that long-term use of smoking cessation medications is preferable to continuing tobacco use although it stops short of formally endorsing long-term use

NRT. Nevertheless, long-term use of NRT has not been shown to cause adverse effects. According to the smoking cessation guidelines from the U.S. Public Health Service, some smokers may need NRT treatment for longer than 3 months, and quitters who feel they may need longer treatment are advised to talk to their doctors. [230]

Will participants who smoke concurrently with NRT use be exposed to increased nicotine? It is possible that participants may smoke while using NRT. Approximately half of the users of transdermal nicotine patch smoke concurrently with treatment. It is unlikely that concurrent smoking will adversely affect patients. [236] Nicotine patch doses of up to 63 mg/day have been shown to be safe with respect to the cardiovascular system even with concomitant smoking. [256] In a study of 5 day trials of 21, 42, and 63mg/day nicotine patches combined with ad lib smoking, there were no changes in blood pressure, heart rate, changes in the pattern of circadian variations, fibrinogen or lipid profiles with NRT dose. Urinary epinephrine level was significantly higher with transdermal nicotine than with no nicotine but was not higher with transdermal nicotine combined with smoking compared with smoking alone. While it is generally believed that patients with unstable coronary heart disease may be at risk from concurrent smoking and NRT, it is unclear whether this risk is greater than the risk of smoking alone. [257] The doses of nicotine obtained by regular cigarette smoking generally exceed those delivered by NRT, and the cardiovascular effects of nicotine are, in general, more intense when delivered rapidly by cigarette smoking than the slower delivery by transdermal nicotine patch or nicotine gum. [238] Cigarette smoking also increases blood coagulability, a major risk factor for acute cardiovascular events, whereas transdermal nicotine does not do so. Clinical trials of NRT in patients with underlying, stable coronary disease suggests that nicotine does not increase cardiovascular risk. [258] At worst, the risks of NRT are no more than those of cigarette smoking. The risks of NRT for smokers, even for those with underlying cardiovascular disease, appear to be small and substantially outweighed by the potential benefits of smoking cessation. [238]

Nicotine Lozenge is the newest NRT product to be approved by the FDA. Lozenges release nicotine as they slowly dissolve in the mouth. Biting or chewing the lozenge will cause more nicotine to be swallowed quickly and result in indigestion and/or heartburn. They are available in 2mg or 4mg doses. Maximum dosage should not exceed 20 lozenges per day. Participants in the trial will be provided with 2 mg lozenges with instructions to use not more than 9 per day. Each lozenge lasts about 20-30 minutes and nicotine will continue to be absorbed for a short time after the lozenge has disappeared. Participants will be advised not eat or drink 15 minutes before using the lozenge or while the lozenge is still in the mouth. The most common side effects of lozenge use are: soreness of the teeth and gums, indigestion and throat irritation. Because of ease of use and issues using gum with poor dentition common in our population, we will encourage use of NRT lozenges but will provide nicotine gum to those who prefer this form of short acting NRT.

2. Bupropion SR is an aminoketone antidepressant whose safety and efficacy in the treatment of depression and treatment of nicotine dependence has been well documented. Varenicline, NRT and bupropion taken over long periods are likely to be much safer than cigarette smoking. Maintenance pharmacotherapy to reduce harm or aid sustained abstinence has been demonstrated with bupropion, varenicline and NRT. [223,259,260] The experience with long-term use of bupropion for depression suggests that it is well tolerated.

In trials of bupropion for smoking cessation in stable outpatients with schizophrenia published to date, bupropion treatment was not associated with worsening in any psychiatric symptom domain. [24,26,28,29,51,87] Bupropion independently improves attention during a smoking cessation attempt, [88] and is thought to increase the firing rates of noradrenergic neurons and to cause regionally specific increases in extracellular dopamine concentrations. [261] The sustained release preparation (Wellbutrin SR, Zyban) provides a better safety profile and more convenient dosing schedule than the immediate release product.

Based on efficacy for smoking cessation and tolerability, [262,263] bupropion SR was approved by the FDA in May 1997 as an aid for smoking cessation. Following its release in the U.S. in 1989, clinical and post-marketing surveillance clearly demonstrated that bupropion is well tolerated by the great majority of patients. [264] The maximum recommended dose for bupropion SR is 450 mg per day in divided doses. The most common side effects are dry mouth, headache, insomnia, nausea, tremor, and dizziness. [265] In analysis of

>3000 patients, bupropion SR up to 300 mg/day was associated with seizure rate of 0.06-0.1%.[265] Subjects tolerated bupropion SR 300 mg/d well in large published clinical trials for smoking cessation. [222,262] In the study by Hurt and colleagues, the most common side effects were dry mouth, insomnia, headache and rhinitis, and only insomnia and dry mouth occurred more frequently with SR bupropion than placebo. Only 8% of subjects on bupropion SR stopped the study due to side effects compared with 5% in the placebo group. In a comparison of bupropion SR 300 mg/day with or without added NRT, 449 subjects received bupropion SR 300mg/day. [222] Fifty-seven subjects on bupropion stopped treatment because of adverse events: 29 in the bupropion group (11.9 %), and 28 in the combined-treatment group (11.4 %). The most common adverse events were insomnia and headache.

The most serious adverse effect of bupropion is seizure. This risk of seizure, directly related to peak blood levels of drug, is less with the sustained release preparation, which produces lower peak blood levels of bupropion than the immediate release formulation. There have been no reported seizures in trials of bupropion SR for smoking cessation. The incidence of seizure in clinical trials of bupropion SR for depression at doses of 300 mg/day is 0.1%, based on data from 3100 subjects. [263] The risk of seizure is associated with predisposing factors such as history of seizure, CNS tumor, excessive use of alcohol, abrupt withdrawal from alcohol or other sedatives, addiction to opiates, cocaine or stimulants. What are possible health risks of 18 months of continued bupropion? They are considered minimal.

3. Varenicline is a partial alpha4beta2 nAChR agonist and a full alpha 7 nAChR agonist that was approved by the FDA in 2006 as a pharmacotherapeutic smoking cessation aid. Varenicline is highly effective for smoking cessation, with a pooled RR for continuous or sustained abstinence at ≥6 months of 2.27 (95% CI 2.02-2.55, 14 trials 6166 people). Limiting the analysis to the 9 studies with 12-months follow-up still yields a highly significant effect estimate vs. placebo, (RR 2.23, 95% CI 1.93 to 2.58). Varenicline is also effective for smoking cessation at reduced doses, relevant for those who experience intolerable nausea or other adverse events at the standard dose of 1 mg bid, RR is 2.09 at reduced or variable dose (95% CI 1.56-2.78, 4 trials, 1272 people). Varenicline is superior in head to head comparisons with bupropion, with a RR for abstinence at one year for varenicline vs. bupropion of 1.52 (95% CI 1.22-1.88, 3 trials 1622 people). In the 2012 Cochrane review: Nicotine receptor partial agonists for smoking cessation, only one study of varenicline for smoking cessation in SMI was included, a trial testing the safety and efficacy of varenicline in people with schizophrenia or related disorders at 24 weeks, and it yielded a RR of 5.12, but with a confidence interval of 0.68 to 38.69 it fell slightly short of a statistically significant result. [30,266]

Varenicline was effective and well tolerated for long-term abstinence in trials that tested the use of varenicline for 12 months. [67,223,267] A long-term safety trial found 12-months treatment with varenicline vs. placebo was well tolerated and highly effective for smoking cessation throughout the 52-week treatment period, with a 53-week follow-up RR for seven-day point prevalence abstinence of 4.91 (95%CI 2.56 to 9.42). [267] Varenicline was well tolerated in a trial of 52 weeks maintenance therapy with varenicline or placebo in a group of adults with schizophrenia spectrum or bipolar disorder who were able to attain abstinence during a 12-week open-label phase with varenicline and CBT. [67] In this trial 43% attained abstinence with open smoking cessation treatment, and those assigned to varenicline maintenance treatment had higher abstinence rates at every post randomization visit through 40 weeks of relapse prevention treatment and 24 weeks of follow up. Maintenance treatment tripled both point prevalence and continuous abstinence rates at week 52. Those assigned to maintenance treatment with placebo had a median time to relapse of < 4 weeks while those assigned to varenicline had a median time to first lapse or relapse of 24 weeks. During the follow up phase of the maintenance treatment trial, although 68% of those randomized to varenicline remained abstinent on varenicline at week 52, half of these relapsed during the first three months after discontinuation of maintenance treatment. This trial showed that behavioral treatment alone is not sufficient to maintain abstinence in those with schizophrenia or bipolar disorder who attain abstinence with 12-weeks of pharmacotherapy and CBT, and that even after one year of abstinence, a substantial portion of those who maintained abstinence relapse after treatment discontinuation. This is in line with high early relapse rates reported immediately following discontinuation of pharmacotherapy with bupropion + NRT in adults with schizophrenia. [51] It is also in line with results of varenicline for smoking cessation in 60 outpatient smokers with stable treated bipolar disorder, 15/31

on varenicline vs. 3/29 on placebo were abstinent at the end of 12 weeks treatment, a highly significant difference, [68] however 50% of those abstinent at end of treatment on varenicline relapsed within 3 months of treatment discontinuation and half of these relapsed within 2 weeks of discontinuation of pharmacotherapy, suggesting need for maintenance treatment to maintain abstinence in this population. [268] Thus maintenance treatment with varenicline has been used in clinical trials for 6 months (1 trial) and 12 months (2 trials, 1 in smokers with schizophrenia and bipolar disorder) and has been found to be well tolerated and effective in all 3 maintenance treatment trials, though relapse rates after discontinuation of pharmacotherapy was rapid and high after 52 weeks treatment in smokers with schizophrenia and bipolar disorder. Thus there is strong rationale for the safety for and likely positive therapeutic benefit of treatment with varenicline for up to 18 months in the proposed trial.

Despite worrying post marketing case reports of serious psychiatric adverse events with varenicline, evidence for safety of varenicline in treated outpatients with schizophrenia, bipolar disorder, and major depressive disorder from placebo controlled RCT's and case controlled trials is mounting rapidly. [60,63,67,85,269-271] There have been reports of depressed mood, agitation, behavioral disturbance, suicidal ideation, worsening of psychotic symptoms and suicide in people attempting to quit smoking with varenicline. The role of varenicline in these symptoms from uncontrolled case reports is not known, and, while the FDA is investigating these reports and has ordered further study of varenicline in smokers with psychiatric illness, as yet, no information is available on rate of occurrence or likely association with varenicline. Because of reporting bias, confounding, uncertain denominator, causality and even adverse event rates are impossible to infer from such reports. The underlying disease of nicotine dependence or process of smoking cessation could be the causal factor. Controlled trials are needed to establish causality, and all controlled trials to date support the safety of varenicline in those with psychiatric illness. No large controlled trial has shown a signal for varenicline to increase psychiatric adverse events over placebo or other active treatment (NRT or bupropion). Psychiatric adverse events have not been associated with varenicline treatment in placebo controlled clinical trials involving over 8,000 individuals or in case controlled trials in over 117,000 individuals. [62,63,270,272] Varenicline has also not been associated with an increased incidence of adverse psychiatric events in prospective [59,61,273] or placebo controlled trials in people with psychiatric illness [274] such as schizophrenia, [30,60,67,85,271,275] bipolar disorder, [268] or depression. [272,276,277]

No clinically meaningful drug-drug interactions have been identified. Antipsychotic medications have a very low affinity for the alpha4beta2 nAChR and in turn, varenicline displays very low affinity for the target receptors of antipsychotic medications, so that pharmacodynamic interactions are unlikely. In *in vitro* assays, varenicline does not inhibit or induce any cytochrome p450 enzymes tested, so is unlikely to affect metabolism of medications metabolized by these enzymes and does not inhibit human renal transport proteins so is unlikely to affect clearance of renally cleared medications. All participants with schizophrenia spectrum, bipolar, and major depressive disorder will be required to be taking a stable dose of an antipsychotic, mood stabilizing or antidepressant medication respectively to enroll in the study.

Varenicline is cleared via active renal transport by the organic cation transporter that represents 92% of clearance. The elimination half-life is ~ 24 hours. Hepatic metabolism of varenicline represents <10% of its clearance, as such, drugs known to affect the cytochrome p450 enzymes are not expected to have a clinically meaningful effect on varenicline exposure. No clinically meaningful effects of age, gender, or race have been identified on varenicline metabolism. Varenicline clearance is reduced in those with severely reduced renal function. As recommended, those with impaired renal function will be started on a varenicline dose of 0.5 mg per day and will receive a maximum of 0.5 mg bid as tolerated or may be preferentially prescribed bupropion and NRT. Those on dialysis will not be included in this study, as their weight cannot be measured accurately.

The most common adverse effect associated with varenicline use is nausea, which occurs in ≥30% of those who take the drug. Most nausea associated with varenicline use is mild or moderate, dose-dependent and transient. [266] In registration trials, vomiting occurred in 5% of participants, compared with 2% for placebo. Most are able to tolerate nausea that is not associated with vomiting and are encouraged to take the

medication with food and at least 8 ounces of water to reduce incidence and severity of nausea. In people with persistent nausea, dose reduction to varenicline 0.5 mg bid or switch to bupropion and NRT will be offered.

Because varenicline is expressed in the milk of animals and because of its potential for adverse effects on infant development, breastfeeding mothers will not be enrolled in the trial. Varenicline use has been associated with reduced fetal weights in animal studies. It has been assigned to Pregnancy Category C. Thus pregnant women will be excluded from this study, and pregnancy status will be biochemically verified with urine HCG measures in each participant of childbearing potential. Because of the potential benefit of smoking cessation on fetal development, pregnant women will be referred for alternative smoking cessation treatments.

B. Risks due to smoking cessation

1. Nicotine Withdrawal Symptoms. Study participants may experience nicotine withdrawal symptoms. These include anxiety, restlessness, anger, irritability, sadness, difficulty concentrating, increase in appetite, weight gain, difficulty sleeping and craving for tobacco. [278,279] Withdrawal symptoms begin within a few hours and peak 24-48 hours after cessation and last an average of 4 weeks. [278] Cessation of smoking can cause slowing on EEG, decreases in cortisol and catecholamine levels, [280] sleep EEG changes, and a decline in metabolic rate. The mean heart rate decline is about 8 beats per minute, and the mean weight gain is 3-5 kg. [231] As with all withdrawal syndromes, the severity varies among subjects. Cessation of smoking can produce clinically significant changes in the blood levels of several medications. [281] This effect appears to be due, not to nicotine, but rather to the effects of benzopyrenes and related compounds on the P450 system. Withdrawal symptoms can also mimic, disguise, or aggravate the symptoms of other psychiatric disorders or side effects of medications.

2. Depressive Symptoms Following Smoking Cessation. We consider the likelihood of developing a severe depressive episode to be mildly elevated beyond baseline for this population during the trial, though it is not likely mediated by smoking cessation. However, our monitoring will help ensure that the development of depressive symptoms is detected at an early stage.

While Glassman and Covey reported increased risk for recurrence of MDD with abstinence up to 6 months post cessation in those with past MDD [282] this study was hampered by differential dropout in the non-abstinent group. Recent studies have reported no increased risk for recurrence of MDD post cessation (i.e., no abstinence status by MDD history interaction in three studies). [283-285] In fact, MDD history, not abstinence status at end of treatment, associated with recurrence of MDD post quit attempt. [283,285-287] MDD history positive smokers have greater increase in mood disturbance after a quit attempt and may benefit from behavioral treatment and ongoing treatment for depression and nicotine dependence as will be provided in this trial. [288] While MDD history, and not abstinence at end of treatment, is associated with recurrence of MDD post quit attempt, the risk of continued smoking in this population is known, and is high, and the benefit of cessation is clear and large. [48-50]

17. ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and informed consent. Procedures for recruitment, consent, intervention, data collection and analysis will be reviewed and approved by the Johns Hopkins, Massachusetts General Hospital and Sheppard Pratt (Family Services Agency, Inc.) Institutional Review Boards and the DSMB. Recruitment for the study will include posters posted around each facility, flyers and brochures, and announcements and presentations at regular staff meetings at all facilities and consumer meetings (at the psychiatric day programs). We will also show an informational video. . We will work with rehabilitation staff to identify potential participants by reviewing their list of program attendees with them. We plan to mail letters to potentially eligible consumers to tell them about the study. We will obtain a HIPAA waiver and work with mental health program staff to identify potential participants by reviewing their list of program attendees with them. Rehabilitation counselors and mental health clinic staff may mention the trial to their consumers. Interested individuals will be directed to contact us by phone or in person at the day program or clinic. Patients will be reminded that their continued participation in the rehabilitation program or attendance at outpatient clinic is not conditional on enrolling in the study.

We will use a two-stage consent procedure: one consent form will be signed upon entry that covers screening and baseline data collection for the study. Another will be signed at the time of randomization. The consent forms will detail the purpose of the study, the requirements for participation, and the potential benefits and risks. We will work with the IRB to include appropriate language and protections in accordance with the data sharing policy. In consenting individuals to participate in the study, the following procedures will be used: 1) Procedures involved in the study will be fully explained to participants by study staff trained in informed consent procedures for persons with serious mental illness. 2) Participants will complete a brief test of comprehension of study procedures to demonstrate that they understand the risks and benefits of study participation and clearly consent, before consent is accepted. Any wrong answers are corrected and additional information given to clarify, until a person can easily answer all items successfully or they indicate they do not wish to continue. 3) Those agreeing to participate will sign the consent form.

Protection against risk: General

Participant safety will be closely monitored. The safety approach will be implemented similar to the investigators' other trials (e.g., ACHIEVE).[67,69,71,106,125] We have a medical safety officer, Dr. Miller, a practicing internist, who will work with Drs. Daumit and Evins to promote and monitor safety throughout the study. The safety officer does not provide direct medical care and is not involved in the intervention.

Hypoglycemia, hypotension or other potential consequences of improved health behaviors or changes in medication for hypertension or diabetes mellitus will be minimized by having the intervention team communicate closely with the primary care physician and mental health program staff about medication changes, exercise participation and coordinate assistance for participants with blood sugar monitoring. For example, if an active intervention group participant is taking a sulfonylurea and has significantly increased exercise frequency, the intervention team will communicate with the primary care physician and suggest a glucose-lowering agent that would have lower risk of hypoglycemia, such as metformin. The health coach will also communicate with the primary physician after medication changes.

Physical activity will be moderate and monitored: The risk of physical activity will be minimized by emphasizing moderate (as opposed to vigorous) activity, and by following American College of Sports Medicine guidelines regarding need for medical examination prior to beginning an exercise program.[229] Participants who wish to progress to vigorous activity will be advised to obtain approval from their primary care physician. Risk of injury is further minimized by instruction on proper exercise technique, proper use of exercise equipment, the importance of warm-up and cool-down exercises, and proper stretching techniques.

Blood drawing: All phlebotomy will be performed by an experienced phlebotomist. Participants will be given information on how to contact a study clinician (Dr. Miller or Dr. Daumit) if complications occur.

Extreme weight loss methods will be discouraged. The interventionist and mental health program staff will be aware of the possibility that intervention subjects could use extreme methods to lose weight. Study staff will discourage extreme calorie restriction or unbalanced diets, as these may lead to inadequate energy intake or lower than recommended intake of essential nutrients. Participants will be reminded regularly of the importance of safe weight loss. Those who have a sudden, marked weight reduction will be interviewed to determine if extreme measures have been taken. The intervention staff will be trained to detect evidence of extreme measures and will be given strategies for responding.

Minimizing risks associated with use of NRT, bupropion and varenicline. The participant's primary psychiatrist, primary care physician, Dr. Miller (safety officer) and Dr. Evins will be aware when pharmacologic treatment for smoking cessation is initiated by the prescribing psychiatrist. For example, we will discuss safety of NRT with the PCP for those who have a history of coronary artery disease or uncontrolled insulin dependent diabetes mellitus. Seizure risk from bupropion will be minimized by not having study psychiatrists prescribe bupropion to subjects with predisposing factors for seizure, including but not limited to ongoing seizure disorder, treatment with clozapine at ≥500mg/day without a therapeutic dose of an anticonvulsant medication, or head injury with loss of consciousness or other sequelae. Additionally, the risks of combining other

antipsychotic medications that may lower the seizure threshold and the risk of seizure with bupropion SR may be additive and will be considered by the prescribing physician. In addition, as there are choices of pharmacotherapy for smoking cessation in this study, when a participant is ready to initiate pharmacotherapy, the prescribing psychiatrist will consider the safest choice given the individual participant's profile. Weekly for the first 4 weeks and then at least twice a month the health coach will administer the Minnesota Nicotine Withdrawal Scale [289,290]and ask participants if they have had any unanticipated visits to a health care provider, suicidality, homicidality or changes to doses of medications. These will serve as safety screens. If there are any concerning psychiatric symptoms or other issues, the health coach will follow the protocol and communicate with the intervention director and study psychiatrist, who in turn may contact the primary psychiatrist, primary care physician, and/or Dr. Evins, Miller and Daumit.

Minimizing risks due to smoking cessation. Withdrawal symptoms are reduced by pharmacotherapeutic cessation aids (i.e., NRT, varenicline) and by participation in the behavioral intervention that helps participants strategize with coping skills. We expect exercise will also ameliorate withdrawal symptoms. Potential weight gain from smoking cessation will be addressed with the weight management aspects of the intervention that will teach methods for weight control. To minimize the risk of depressive or other psychiatric symptoms associated with smoking cessation, we emphasize that the intervention takes place at participants' own mental health programs, and all participants will be under regular, ongoing treatment with a psychiatrist and a therapist. The health coach under supervision of the intervention director, Dr. Daumit and Dr. Miller will screen participants for concerning symptoms or and will follow a safety protocol including notifying the intervention director and communicating with study psychiatrists, and Dr. Evins, Miller and Daumit. Thus, we will believe any risks will be minimized.

Breach of confidentiality: All participant information will be considered confidential. This confidentiality will be assured through several mechanisms. Each participant will be assigned an anonymous study ID, which will be used on all study forms; all study forms and paper records that contain participant information will be kept in secured, locked areas when not in use. Such materials, when in use, will be kept away from public scrutiny. Forms that need to be discarded will be destroyed. Access to participant information will be restricted to authorized personnel. For computerized study data, access will be password protected. When the study database is ready for analysis, it will not contain identities of participants. During data collection, data collection forms will be stored in locked areas with access only by authorized personnel. Finally, neither the mental health programs nor participants will be identified by name in any publications. Data will not be presented in such a way that the identity of individual participants can be inferred.

Participant reimbursement: Participant reimbursement for data collection for all participants is estimated at $115 total for completing all data collection visits, divided over each visit. Active intervention participants will receive small incentives for group and individual session attendance and for low smokelyzer readings. These will consist of earning points that may be traded in for small gifts, or earning up to $3 for session attendance or smoking abstinence. A participant in the active intervention arm could earn up to $200 over the course of the 18-month study for intervention participation.

Potential benefits of the proposed research to the subjects and others: Potential benefits to the study participants who receive intervention include improved health behaviors and improved cardiovascular risk profiles. All participants receive blood pressure and laboratory test results. Potential benefits to others include the possibility that the research will lead to the dissemination of effective interventions to decrease tobacco dependence and improve overall cardiovascular health in persons with serious mental illness.

Importance of knowledge to be gained: Persons with serious mental illness have high burdens of each major cardiovascular risk behavior, yet persons with SMI have been systematically excluded from interventions to decrease cardiovascular risk. If successful, this proposed integrated smoking cessation, weight management and exercise intervention could be disseminated widely. The minimal health risks to participants are offset by the potential benefits to participants and to the greater population with chronic mental illness.

Data and safety monitoring plan: Protection of research participants begins with the eligibility criteria, which are designed to exclude individuals with serious medical conditions that would preclude their ability to safely participate in the intervention. During the study, clinical care will be provided by the participants' usual specialty mental health providers and the primary care physician, with communication with the study staff. Participants will be made aware of this delineation of responsibility. The exception to this is participants whose primary psychiatrist is the study psychiatrist. Participants in the active intervention will be monitored for psychiatric symptoms by the health coach. Recognizing the opportunity for early detection of clinical problems and the small risk of study-related morbidity, we will perform periodic safety assessments for intervention and control participants. We will inquire about cardiovascular, musculoskeletal, psychiatric and possible medication-related symptoms at 6-month intervals. We will identically apply a process to each randomized group and collect self-reported symptoms, health care utilization and records related to CVD and mental health outcomes, including emergency department use and hospitalizations, and ask standard questions regarding possible medication side effects. Clinically significant results will lead to referral to the primary care physician and/or psychiatrist. Information that comes to the attention of study personnel informally (e.g., through data collection or intervention activities at the center) may also lead to referral. Symptoms that will lead to referral include (but are not limited to) those that suggest cardiovascular disease (e.g., exertional chest pain, dyspnea, presyncope or syncope), uncontrolled hypertension, uncontrolled diabetes, complications of physical activity or psychiatric symptom exacerbation. Participants are also queried at these same time points about possible adverse events (defined below). Positive responses trigger an adverse event (AE) record, which is reviewed and classified as gastrointestinal, cardiovascular, musculoskeletal, psychiatric, or other in nature. This information is then reported to the DSMB. Similar information reported by participants at other times (e.g., during intervention classes) is noted and followed up with as needed to assure participant safety. The following constitute adverse events (AEs): heart attack, stroke, transient ischemic attack, heart failure, coronary angioplasty or bypass surgery, angina pectoris, broken bone, torn ligament, any other serious injury to the bone or muscle, seizure or hospitalization for suicidal or homicidal ideation. Evidence of the occurrence of these events is based on participant self-report that a health care professional has diagnosed the condition. We will attempt to verify the diagnosis through contact with the physician. Though not considered AEs for this study, we also will track and report the incidence of hyperlipidemia, gallbladder disease, diabetes, cancer, emergency department use and hospitalization. All other outcomes that may be construed as being an adverse consequence of study participation, such as an injury while performing a study measurement, are documented, reviewed, and followed up on as needed by a study clinician.

The Data and Safety Monitoring Board will meet at least twice a year during the study. The DSMB members are clinical research scientists not otherwise connected to the study whose expertise includes biostatistics, CVD prevention, mental health and clinical trials. The committee will review the protocol before the start of fieldwork. Adverse events will be reviewed initially by Dr. Miller, Dr. Daumit and Dr. Evins and then reported locally to the IRB, the DSMB and the NIH project office according to prevailing policies of these review bodies. This plan should ensure participant safety.

18. SUBSTUDY OF FACTORS RELATED TO INTERVENTION IMPLEMENTATION

Semi-structured interviews with selected staff

Human subjects involvement and characteristics: To better understand the intervention implementation process and the perspectives of community mental health program leadership and staff, psychiatrists and health coaches at Bayview and Family Services Agency, Inc. and about potential barriers and facilitators of the intervention, perceived effectiveness and plans for sustainability, we will conduct a series of semi-structured interviews. We will conduct interviews at baseline, and then follow-up interviews at the end of study. We expect to conduct interviews with up to 50 people, or a total of 100 interviews.

Sources of materials. The interviews will inquire about perceived effectiveness, ease of or barriers for the intervention, fit within the organization and financial models for continued support. They will be conducted in a private office will be approximately 30 minutes in length and will be audio recorded. Recordings will be transcribed.

Potential risks. Risk of loss of confidentiality is the main study risk. We expect this risk to be very low.

Plans to minimize this risk are described below.

Adequacy of protection against risks

1. Recruitment and informed consent. Procedures for recruitment, consent, and, data collection and will be reviewed and approved by the Johns Hopkins Institutional Review Boards and Sheppard Pratt Institutional Review Boards. We will invite individuals to participate in interviews in person and/or by letter/email, and we will obtain written informed consent for these interviews. We will plan to interview the health coaches, exercise leaders, Family Services Agency and Bayview Psychiatry leadership, study clinicians, and psychiatrists and psychiatric nurse practitioners at the sites. We also aim to interview a purposeful sample of other mental health program staff reflecting a range of responsibilities (e.g., therapist, case manager, rehabilitation program counselors). We anticipate 60% women and 25% African-American in this sample, similar to current employee demographics.

2. Protection against risk:

Breach of confidentiality: All information will be considered confidential. This confidentiality will be assured through several mechanisms. Transcripts of interviews a will have names removed. The tapes will be kept for 7 years and then destroyed. Finally, neither the mental health program nor staff will be identified by name in any publications. Employees will be assured that their participation in the study and information shared in the interviews will not affect their employment or their evaluation.

Participant reimbursement. We plan to give a $50 gift card for each interview.

Potential benefits of the proposed research to the subjects and others: There are no direct individual benefits. Potential benefits to others include the possibility that the research will lead to the understanding of factors that may be important for sustaining and disseminating smoking cessation interventions for persons with serious mental illness in community mental health organizations.

Importance of knowledge to be gained: Persons with serious mental illness have 2-5 times the smoking prevalence, and higher overweight/obesity and physical inactivity than the general population and consequently a high burden of CVD and early death. It is critical to know if interventions to improve their health can be sustained and what factors predict sustainability so that interventions can be translated and optimally spread into the community. The goal of this study is to collect information from staff to understand factors related to sustainability and dissemination. The minimal risks are offset by the potential benefits to populations with chronic mental illness who would benefit from future interventions.

Data and safety monitoring plan: This is an observational study. No interventions are planned. Dr. Daumit will have responsibility for monitoring and oversight of any problems/events for this research.

Surveys with program staff

Human subjects involvement and characteristics: To study factors influencing intervention implementation and possible future dissemination, we will invite all mental health program staff to participate in a survey. These surveys will complement and add to the information we collect from the smaller number of semi-structured interviews (described above), will contain some standard implementation science measures, and will reach a wider range of staff. We aim to invite staff in Bayview Adult Psychiatry programs and Family Services Agency, Inc in the psychiatric day program and clinic to participate.

Sources of materials. The surveys will be available through Qualtrics, or if preferred, on paper. The questions will ask about implementation climate, attitudes towards evidence-based practices, perceptions of the role of mental health and medical health care sectors in addressing clients' somatic health needs; perceptions of the intervention, and potential stigma towards persons with SMI.

Potential risks. Risk of loss of confidentiality is the main study risk. We expect this risk to be very low. Plans to minimize this risk are described below.

Adequacy of protection against risks

1. Recruitment and informed consent. Procedures for recruitment and data collection will be reviewed and approved by the Johns Hopkins Institutional Review Boards and Sheppard Pratt Institutional Review Boards. We will invite individuals to participate in surveys in person and/or by letter/email. We aim to invite staff in Bayview Adult Psychiatry programs and Family Services Agency, Inc in the psychiatric day program and clinic to participate. Individuals could participate in the survey and the interview.

2. Protection against risk:

Breach of confidentiality: All information will be considered confidential. This confidentiality will be assured through several mechanisms. The surveys will not contain names or other identifying information. The mental health program and staff will be identified by name in any publications. Employees will be assured that their participation in the study and information shared in the survey will not affect their employment or their evaluation.

Participant reimbursement. We plan to give a $25 gift card for each survey.

Potential benefits of the proposed research to the subjects and others: There are no direct individual benefits. Potential benefits to others include the possibility that the research will lead to the understanding of factors that may be important for sustaining and disseminating smoking cessation interventions for persons with serious mental illness in community mental health organizations.

Importance of knowledge to be gained: Persons with serious mental illness have 2-5 times the smoking prevalence, and higher overweight/obesity and physical inactivity than the general population and consequently a high burden of CVD and early death. It is critical to know if interventions to improve their health can be sustained and what factors predict sustainability so that interventions can be translated and optimally spread into the community. The goal of this study is to collect information from staff to understand factors related to sustainability and dissemination. The minimal risks are offset by the potential benefits to populations with chronic mental illness who would benefit from future interventions.

Data and safety monitoring plan: This is an observational study. No interventions are planned. Dr. Daumit will have responsibility for monitoring and oversight of any problems/events for this research.

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