Integrated Smoking Cessation Treatment for Smokers with Serious Mental Illness
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DETAILED PROTOCOL

Integrated Smoking Cessation Treatment for Smokers with Serious Mental Illnesses
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I. BACKGROUND AND SIGNIFICANCE

Addiction to tobacco-derived nicotine is highly prevalent among those with serious mental illness (SMI). Fifty years after the first United States (US) Surgeon General's report of an association between smoking and cancer, adult smoking in the US has declined by 55% in the general population, to 18% [1-3]. Despite availability of smoking cessation treatments, specifically effective in this population, comparable decreases in smoking rates have not occurred among smokers with SMI [4]. Smoking prevalence among adults with SMI in the US is higher today, at 53%, than it was in the general population in 1964 [5, 6]. The 7.3 million adults with SMI in the US who smoke tobacco [7, 8], comprise 2% of the US population but 13% of smokers in the US [8]. Recent estimates indicate that 64%-79% of those with schizophrenia spectrum disorders smoke tobacco regularly [6, 9], as do 44-71% of those with bipolar disorder [6, 9, 10], and 43% of those with major depressive disorder [11], and most state they would like to quit but have not been offered treatment to help them quit [12-14].

Tobacco smoking is associated with significant morbidity and premature mortality in those with SMI. People with SMI in the US suffer physical diseases at younger ages and die approximately 28 years earlier than those without mental illness, primarily from diseases directly attributable to tobacco smoking [15, 16]. Premature mortality in those with SMI is the largest lifespan disparity in the US [17, 18]. While tobacco smoking was responsible for over 18% of all deaths in the US in 2000 [19, 20], half of all deaths in the state of California in those who had been hospitalized for schizophrenia, bipolar disorder, or major depressive disorder were due to one of 19 diseases identified by the Centers for Disease Control and Prevention (CDC) as being causally linked to tobacco use [21].

Previous studies supporting the proposed research.

Smoking Cessation in SMI: There is abundant evidence that most smokers with SMI want to quit smoking [12-14], and extensive clinical trial evidence for efficacy and tolerability of first-line pharmacotherapies for smoking cessation specifically for those with SMI [22-37], confirmed in independent, systematic reviews and meta-analyses [28, 29, 38, 39] and incorporated into clinical practice guidelines that recommend that providers prescribe pharmacotherapy for smoking cessation with behavioral support for all smokers with schizophrenia spectrum disorders who wish to try to quit [40]. There is robust evidence for efficacy for bupropion alone and in combination with nicotine replacement therapy (NRT) in randomized, placebo-controlled trials for those with SMI who wish to quit smoking [22-24, 26, 30-32, 41, 42], confirmed in independent meta-analyses [28, 29], and integrated in the 2010, National Institute of Mental Health sponsored Schizophrenia Patient Outcomes Research Team (PORT) Guidelines for evidence-based treatment of smokers with schizophrenia [40].

There is also strong and growing evidence for safety and efficacy of varenicline for smoking cessation specifically in those with SMI that has emerged since the PORT Guidelines were published in 2010. Contrary to anecdotal reports, no controlled trial to date has shown a signal for increased neuropsychiatric adverse events other than sleep disturbance with

varenicline compared to placebo, bupropion or NRT [28, 33-37, 43]. Much of this evidence has been added as supplemental data in the FDA prescribing information and will be reviewed in an upcoming FDA special advisory board meeting to consider removal or modification of the black box warning. In a randomized controlled trial in 60 smokers with bipolar disorder, those who received varenicline were 8-fold more likely to quit smoking by the end of 12 weeks treatment and 3-fold more likely to be abstinent at a 6-month follow up than those assigned to placebo and behavioral support [34]. Our group found abstinence rates of 42% with 12 weeks open label varenicline among 203 smokers with SMI [37], and among those who attained abstinence in this trial, those who received maintenance varenicline were 6-fold more likely to be abstinent at 52 weeks than those who switched from varenicline to identical placebo after 12 weeks of treatment [37]. In smokers with current or past major depressive disorder, varenicline more than doubled continuous abstinence rates over placebo at the end of 12 weeks treatment and 6-month follow up [33]. In combined data from two trials in 137 smokers with schizophrenia spectrum disorder, those assigned to varenicline were 4-fold more likely than those on placebo plus behavioral support to have attained abstinence, RR=4.74, 95% CI 1.34-16.71 [28, 36, 43]. Varenicline has been shown to be statistically significantly superior to bupropion or NRT for smoking cessation in the general population [44-50], and increasing evidence suggests it is also superior to bupropion or NRT for smokers with SMI [36, 39, 51].

Despite this evidence, few with SMI are offered advice to quit smoking by their primary care providers, and even fewer are prescribed proven effective tobacco dependence pharmacologic and behavioral treatment [52-59]. For example, in a survey of 685 smokers with bipolar disorder, 74% expressed intention to quit smoking, while only 33% had been advised to quit by a healthcare provider [59]. However, it is not known whether interventions designed to improve prescriber delivery of evidence-based nicotine dependence treatments to those with SMI in the community will increase smoking cessation treatment delivery or increase tobacco abstinence rates.

System-wide interventions, proven effective in other treatment setting may improve provision of evidence based smoking cessation treatment to those with SMI. Academic detailing to educate providers about the safety and tolerability of smoking cessation treatment and the risk to benefit ratio of providing such treatment vs not providing such treatment in this population is one such potential system wide intervention that, if proven effective, could be instituted on a broad scale. Availability of community health worker support to patients and providers, as an additional component of the psychiatric rehabilitation team and liason between psychiatric rehabilitation and primary care services is another potential system-wide intervention that could improve outcomes that has shown benefit in other circumscribed roles.

Rationale for the proposed research.

The benefits of smoking cessation are dramatic for all age groups [70, 71]. Those who quit smoking between ages 25 and 34 live10 years longer than those who do not quit; those who quit between ages 35 and 44 gain 9 years of life, those who quit between ages 45 and 54 gain 6 years, and those who quit between ages 55 and 64 gain 4 years compared to those who do not quit smoking [71]. Our group has demonstrated that smoking cessation in those with SMI with multiple cardiovascular risk factors drives reduction in cardiovascular mortality risk [72].

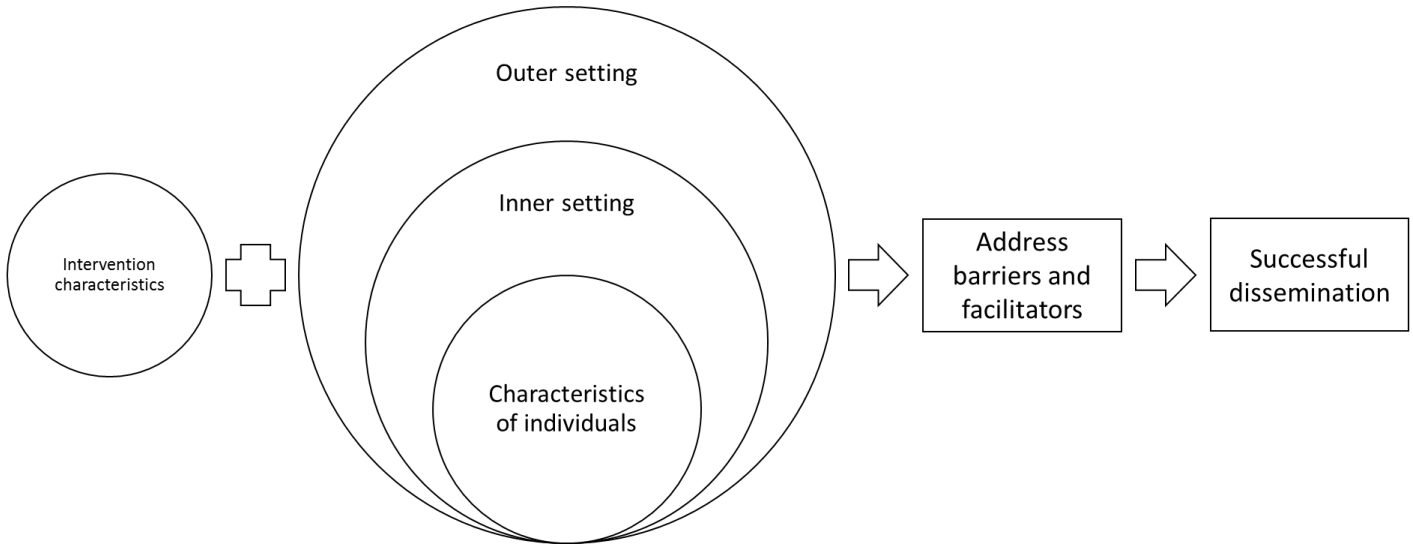
Low rates of provision of guideline-concordant smoking cessation treatment in primary care to those with SMI in the community contribute to the abysmally low rates of smoking cessation and the subsequent mortality disparity in this population [52-54, 56, 57]. Population-

wide smoking cessation rates among adults with SMI are less than half those in the general population [73]. However, 20-48% abstinence rates have been reported in individuals with SMI in clinical trials of standard pharmacotherapies and behavioral treatment [28, 33, 34, 36, 37]. Achievement of these abstinence rates in those with SMI in the community through improved delivery of effective, evidence-based, smoking cessation treatments to those with SMI would result in the elimination of tobacco use among 1.4 to 3 million people with SMI served in community settings such as those proposed in this study, which would dramatically impact the 28-year reduction in lifespan observed in those with SMI [74], largely due to smoking-related cardiovascular disease [15].

Rationale for the Mixed Methods Research for Understanding Barriers and Facilitators to Scaling and Implementing IC Intervention

The successful integration and future dissemination and scale-up of the IC intervention (AD+CHW) to improve delivery of evidence-based treatments (EBTs) for smoking cessation in smokers with SMI necessitates the identification of barriers and facilitators to better understand the factors that impact the integration of IC and EBTs in routine clinical care. The results will aid the development of strategies to successfully address key barriers that may hinder future initiatives for the systematic implementation and effective dissemination of these interventions One strategy to increase the effectiveness of integrating evidence-based interventions in routine clinical settings is to capitalize on both researchers' and stakeholders' knowledge and experiences to ensure the fit between the intervention, training provided, stakeholder needs, and organizational context. Previous work suggests that barriers are present at several levels, including organizational-level barriers, such as lack of time, funds, provider-level barriers, such as perceptions of IC and EBTs and their fit with the needs of patients, and patient-level barriers, such as stigma and knowledge of availability and accessibility of IC components such as CHWs and EBTs. Therefore, models that capture such potential variables while providing a framework to characterize the process and outcomes of integrating these interventions are essential.

Figure 1. Theoretical framework using the CFIR

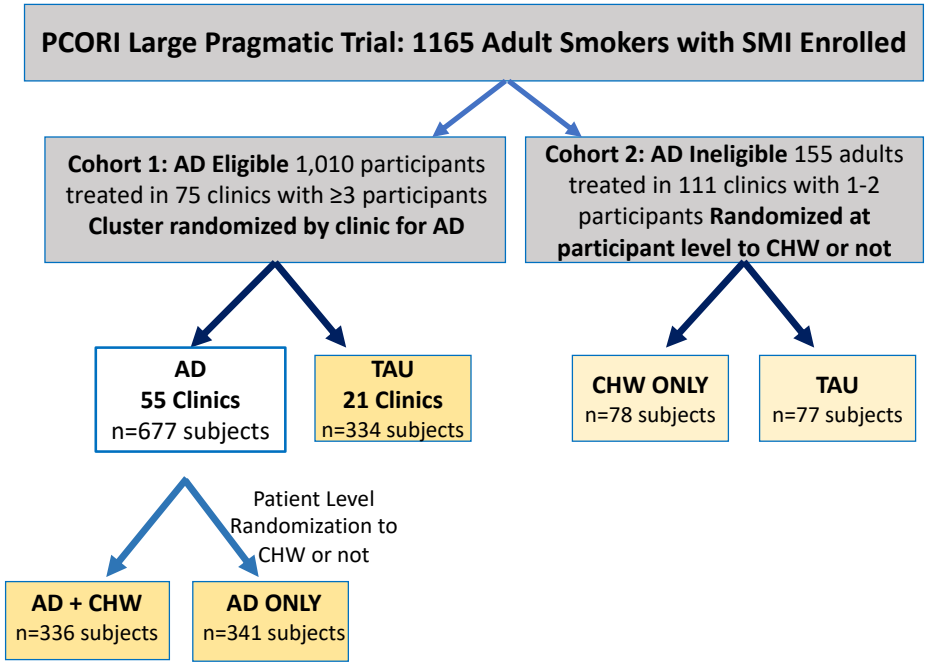


As such, the current proposal will rely on the Consolidated Framework for Implementation Research; The CFIR is a "meta-theoretical" implementation framework generated specifically for research in health care that draws upon 19 different implementation models, to create a typology of constructs that guides different phases of implementation studies (see Figure 1). The CFIR constructs have been extensively used across settings and populations, and provide a practical guide for the systematic assessment of barriers and facilitators when implementing interventions. Specific CFIR variables that have previously been shown to impact the successful integration of evidence-based treatments as well as those that have been barriers to and facilitated future scale-up and dissemination strategies will be studied to address the aims of the current study.

In this study, we aim to test whether a provider-level educational intervention in the form of targeted, practical, action-oriented education to primary care physicians and nurses on safety and effectiveness of and how to use evidence-based smoking cessation treatment for those with psychiatric illness, termed academic detailing (AD), alone or in combination with practical support offered to the primary care physician / primary care team and the smoker with SMI in the form of a community health worker (CHW) will improve recommendation and utilization of standard of care smoking cessation treatments to and by those with SMI and, if so, whether the intervention improves smoking cessation rates for adults with SMI who smoke.

In addition, we aim to systematically identify and define barriers and facilitators to implementation of components of the integrated care intervention in primary care clinical settings using an interactive convergent mixed-methods design.

To do so, we will randomize primary care clinics that serve 3 or more, out of the approximately 1300 adult smokers with SMI who receive psychiatric rehabilitation services, Community Based Flexible Support (CBFS) or Assertive Community Treatment (ACT)), from the two largest providers of these services in the Boston area to either receive AD for their prescribers or not in a cluster randomized design. Half of the smokers with SMI in the study who receive primary care at the clinics assigned to the AD intervention to providers will be randomly assigned to be offered CHW support in addition to their ongoing psychiatric rehabilitation (CBFS or ACT) services. For participants who receive primary care from a clinic that serves two or fewer adult smokers with SMI, we will randomize half to receive CHW services and half to treatment as usual. See revised Schema below.



II. SPECIFIC AIMS

In this cluster randomized study with embedded secondary randomization, comparing AD+CHW, AD, CHW and TAU, we seek to achieve the following aims:

Aim 1. Discover whether the AD+CHW intervention increases prescriber provision of advice and assistance to quit smoking and improves tobacco abstinence rates in smokers with SMI compared with usual care (TAU).

Hypothesis 1a. Smokers with SMI who receive AD+CHW will report higher rates of biochemically verified tobacco abstinence than those assigned to TAU at the Year 3 Assessment. This is the main outcome measure.

Exploratory hypotheses regarding effect of individual components of the intervention on abstinence rates:

Hypothesis 1b. Participants assigned to receive AD+CHW will demonstrate higher rates of biochemically-verified, 7-day point-prevalence tobacco abstinence than those assigned to AD at the Year 3 Assessment.

Hypothesis 1c. Participants assigned to receive AD will demonstrate higher rates of biochemically-verified, 7-day point-prevalence tobacco abstinence than those assigned to TAU at the Year 3 Assessment.

To include participants from Cohort 2, we include a secondary, factorial analysis using cohort as a factor, that was planned when we randomized participants whose clinics cared for ≤2 participants.

Hypothesis 1d. Participants assigned to receive CHW will demonstrate higher rates of biochemically-verified, 7-day point-prevalence tobacco abstinence than those assigned to TAU at the Year 3 Assessment.

Aim 2: Discover the effect of the AD+CHW interventions on patient-reported overall health, as measured by the SF-1, compared with TAU.
Hypothesis 2. Participants assigned to receive AD+CHW will report greater improvement in their overall health at their Year 3 Assessment compared to Baseline than those assigned to TAU.

Exploratory Aim 3: Evaluate feasibility of the AD+CHW intervention and assess factors that could impact implementation on a national scale.
Hypothesis 3. Identify differences in care processes between AD+CHW and TAU that may be suggestive of specific mechanisms.

Exploratory Aim 4: Evaluate subgroup differences in rates of biochemically-verified, 7-day point prevalence tobacco abstinence among participants diagnosed with schizophrenia and schizoaffective diagnoses compared to participants with other diagnoses.
Hypothesis 4a. Participants with schizophrenia and schizoaffective diagnoses will demonstrate lower absolute rates of biochemically-verified, 7-day point-prevalence tobacco abstinence compared to those with other diagnoses
Hypothesis 4b. Participants with schizophrenia and schizoaffective diagnoses will a demonstrate larger effect of treatment (AD+CHW) vs no treatment (TAU).

Aim 5: Systematically identify and define barriers and facilitators to implementation of components of the integrated care intervention in primary care clinical settings using an interactive convergent mixed-methods (qualitative and quantitative) design.
MRQ 1a. Among patient participant, CHW and primary care provider (PCP) stakeholders, what are the barriers and facilitators to use of the intervention and how do these compare according to performance level, namely, patient quitters, PCP prescribers, and CHW facilitators?
MRQ 1b. Among patient participant, PCP, and CHW stakeholders, what are the barriers and facilitators to use of the intervention and how do these compare according to level of engagement?
MRQ 2a. How do the PCPs, grouped by primary care clinic, differ by performance level and how do their experiences with the intervention, and the barriers and facilitators compare across these groups?
MRQ 2b. What is the association between engagement with the AD intervention among high or low performers, and how did barriers and facilitators experience compare across these groups?
QQ (Qualitative Question) 3. What barriers and facilitators do stakeholders, such as clinical, payor and policy leaders anticipate impacting the implementation of the integrated smoking cessation treatment?

III. SUBJECT SELECTION

The intervention will be implemented at the primary care clinic level. Providers at primary care clinics that provide care to smokers with SMI who receive psychiatric rehabilitation through the CBFS and ACT programs administered through Bay Cove Human Services in Boston and Vinfen Corporation in Cambridge will be identified by the agencies, Bay Cove and Vinfen and

randomly assigned to receive either AD for smoking cessation treatment to those with SMI or no intervention (TAU). We estimate that approximately 26-30 clinics will be assigned to AD and 13-15 to TAU. Patients who receive primary care through clinics assigned to the AD intervention will be randomized to be offered support from a CHW (AD+CHW) or not (AD).
As noted above, after enrollment was complete, but before the randomization, the protocol was amended because 13% (155 of 1165) of enrolled participants received primary care at 111 clinics that each served ≤2 enrolled participants. Because it was beyond the scope of the project to provide AD to so many clinics, prior to randomization, the decision was made and approved by the sponsor to include these 155 enrolled participants in a second cohort in a stratified randomization, such that Cohort 1 (AD-eligible) comprised participants seen in primary care clinics serving ≥3 enrolled participants described above. Cohort 2 (AD-ineligible) comprised participants whose primary care clinic served ≤2 enrolled participants who were randomized to CHW or TAU in a 1:1 ratio.

The patient population will consist of approximately 1300 adult outpatient smokers with SMI who receive psychiatric rehabilitation services through CBFS and ACT programs at Bay Cove Human Services and Vinfen Corporation. This includes adults primarily with schizophrenia spectrum disorders and bipolar disorder.

Inclusion/exclusion criteria:

Primary care clinics/physicians/nurses/care team: There are no requirements for clinics to be included or excluded except that they provide medical care to people with SMI who smoke and who are served by the CBFS and ACT psychiatric rehabilitation systems of Bay Cove and Vinfen. There are no exclusion criteria for prescribers related to specialty (e.g. internal medicine, psychiatry, pulmonary medicine, family medicine, clinical nurse specialist), experience with smoking cessation therapies, or experience working with people with SMI.

Since the patient and their prescriber will decide together on the timing of initiation of any pharmacotherapeutic cessation aid, there will be no exclusion criteria for patients due to medical illness or psychiatric symptom severity or stability or substance use.

To identify and define barriers and facilitators, data will be collected across all key stakeholder levels that have been shown to impact the effective integration of interventions, as well as future dissemination efforts, including participants that are considered “end-users” of the intervention, such as patients, providers/PCPs, community health workers (CHWs) as well as participants that are positioned in roles to elicit change at organization and policy levels, such as organization leadership members and policy and payer leadership members including government officials.

IV. SUBJECT ENROLLMENT

As part of usual care, the CBFS and ACT psychiatric rehabilitation staff track smoking status and the primary care clinics where their clients receive primary care. There are approximately 1300 CBFS and ACT served patients who smoke. As part of their contractually mandated annual psychiatric rehabilitation team meeting, also called an Individualized Action Plan (IAP) meeting, (required by the Department of Mental Health to be conducted by the Human Service Agencies who contract to DMH to provide CBFS psychiatric rehabilitation services), the psychiatric rehabilitation staff will ask their clients if they are willing to answer a 5 minute study survey about their smoking behavior and how their smoking has been addressed by

their primary care team in the past year. Study staff will attend the IAP meeting for those who agree. Study staff will follow a brief script to explain the study to participants, to inform them that participation in the 3 brief annual surveys is entirely voluntary, that their decision of whether or not to participate will in no way impact their ongoing psychiatric rehabilitation services or primary care, and to obtain verbal consent from those who agree to answer the smoking and smoking-treatment-related questions. Participants will be asked to complete the survey on 3 occasions, on an annual basis, once before clinic randomization (Year One, baseline) and twice after the intervention has been implemented (Years 2 and 3). We expect 85-90% of potential participants (n=900) to agree to participate in this 5-minute survey once a year for 3 years at their annual IAP meeting or other setting in which they interact with their psychiatric rehabilitation team members. Those who complete the survey will be reimbursed $5 for their time. Study staff who administer the survey will be trained in the process for obtaining verbal consent, in privacy standards such as the HIPAA privacy rule, and in adherence to the study protocol, including data collection methods.

Procedures protecting confidentiality.

Staff employed at the human service agencies providing psychiatric rehabilitation services (Bay Cove Human Services and Vinfen) will create a database that assigns a study identification number (random numeric value) to each of their clients that they have identified as a smoker. The names of eligible participants under their care and the key linking these names to study IDs will be available only to the psychiatric rehabilitation agency staff. MGH staff who administer the surveys in Years 1-3 will have access only to study IDs and, at the time of the survey, to first names of participants. MGH study staff will identify surveys with study IDs only.

Randomization will be conducted by MGH statisticians and will be based on de-identified data provided by the psychiatric rehabilitation agencies about the primary care clinic and the study ID. Clinics that treat smokers with SMI who agreed to participate in the baseline survey will be randomized. Statisticians will , stratify the randomization by number of participating smokers with SMI treated at the site, Cohort 1 (AD-eligible) comprised participants with primary care clinics serving ≥3 enrolled participants. These clinics were randomized to receive AD to their clinicians or TAU. Participants whose primary care practices were assigned to receive AD were randomized to be offered a CHW (AD+CHW) or not (AD). Cohort 2 (AD-ineligible) comprised participants whose primary care clinic served <3 enrolled participants who were randomized to CHW or TAU. Statisticians will create a field in the database that indicates, for each study ID, the clinic assignment (TAU or AD) and CHW assignment. These databases (one for each psychiatric rehabilitation agency) will be returned to Project Managers at the psychiatric rehabilitation service providers, for use in arranging for CHW support and scheduling of follow up surveys at annual IAP meetings. MGH will be informed of which clinics are assigned to AD for training purposes. At no time will MGH staff be given identifying information for participants.

The following staff are employees at the psychiatric rehabilitation agencies, Bay Cove and Vinfen, and will have a role in the study: Dr. Sally Reyering is co-PI for the project and medical director at Bay Cove, Dr. Don Condie is medical director at Vinfen and a consultant to the project, and 2 clinically trained Project Managers, Bianca Deeb, LICSW is employed at Bay Cove and Lara Sullivan CPH, MSW, LICSW, at Vinfen.. All of the above mentioned staff will complete necessary trainings in human subjects protections. These staff will work with the CBFS teams to identify annual IAP assessment dates for smokers in their teams at which surveys could

take place. These surveys will take place in the community, for example, at day programs, group homes, or psychiatric rehabilitation agency offices where annual meetings take place. Potential participants who, after receiving a verbal summary of the project, including information about the survey, indicate they are interested in participating will have their de-identified survey response entered, including the study ID and question responses, into a secure, mobile, online database (REDCap). The Project Manager at each agency will track completed surveys in their database. In the event that a participant does not attend the scheduled IAP meeting or indicates that he or she would like to consider completing a survey at a later date, a Project Manager will attempt to reschedule the interview. Those who indicate they do not wish to answer the survey questions and do not wish to be asked again will have their study ID removed from the list of participants.

The master databases, one for each agency, will be housed at the respective psychiatric rehabilitation agencies. These will contain the study ID, name, address, primary care clinic, clinic randomization and CHW randomization status, assessment status at the Year 1, 2, and 3 assessment (complete, pending, refused) and any important instructions about contacting the client. This database will contain no study survey data and will not be available to MGH staff. The study database, housed at MGH only, will identify participants only with a study ID and will contain study-related data (Study ID, age at baseline assessment, sex, and survey question responses including smoking status, questions regarding smoking treatment in the prior year). These data will not be linked to or included in the master database.

At the end of the data collection period, the statisticians will receive two de-identified databases (one from each psychiatric rehabilitation agency, each including the study ID for each participant for merging purposes) and a de-identified database from MGH, also with each participant identified only by a Study ID. The statisticians will merge these two files using study ID as a common identifier and conduct statistical analyses to learn whether one or both of the intervention increased provision of smoking related treatment or rates of tobacco abstinence among survey participants.

In order to examine the effect of the study interventions on rates of prescribing smoking cessation medication (i.e. varenicline, bupropion and nicotine replacement therapy) we will receive deidentified MassHealth pharmacy claims data for all study participants who are covered by MassHealth. To maintain the firewall between the human services agencies (Bay Cove and Vinfen) and MGH, we will use a multi-step process to obtain deidentified claims data from MassHealth. First, the human services agencies will send MassHealth a file that contains participants' Study IDs linked with MassHealth ID. Next, MGH will send MassHealth a file with participants' Study IDs linked with a limited set of patient study data including, study arm, dates of Year 1 (baseline), Year 2 (intervention year 1), and Year 3 (intervention year 2) data collection, age group (in ten year increments), gender, race (White, Black, Asian, Other), ethnicity (Hispanic, Not Hispanic), self-reported smoking cessation medication use (varenicline, buproprion, nicotine replacement therapy) at Year 1 (baseline), Year 2 (intervention year 1), and Year 3 (intervention year 2), and self reported abstinence at baseline, year 1 and year 2.

MassHealth will link prescription fill data for smoking cessation medications (January 2015-June 2020) with the limited set of patient study data, but strip all study and the MassHealth IDs before returning the data to MGH. Specifically, MassHealth will create a new encrypted ID for each participant only, which will not be linkable with the main study IDs, thus deidentifying the data we receive and analyze. MassHealth will also replace medication fill dates with flags corresponding to which of the study year windows the medication was filled (year prior to

baseline, baseline-interventionY1, intervention Y1-Y2) and strip exact dates from the file. Thus, we will receive a deidentified file from MassHealth that contains the following information:

Encrypted ID
Coverage indicators (e.g., dual-eligibility, MassHealth plan type (e.g., MCO, FFS))
Death Flag (Y/N) during Post-intervention period
Claims for smoking cessation medications (i.e., varenicline, bupropion, NRT)
- Indicator for fill date during either pre vs. post intervention window
- National Drug Code (NDC)
- Drug generic/brand name
- Quantity filled
- Days supply
- New or refill indicator
- Drug costs (e.g., Medicaid paid amount, Patient paid amount (i.e. co-pay))
- Claim version / Claim denial flag
- Prescribing provider
- Indication of whether prescriptions were refilled

Limited set of patient study data
- Study arm
- Age group (ten year increments)
- Gender
- Self-reported smoking cessation medication use (varenicline, buproprion, NRT) at baseline, Y1, Y2
- Race
- Ethnicty
- Self reported abstinence at Year 1 (baseline), Year 2 (intervention year 1), and Year 3 (intervention year 2)

The use of pharmacy data involves no more than minimal risk to participants. All PHI disclosed to MassHealth will be protected using secure transfer and storage and we will disclose the minimum amount of data necessary (e.g., IDs, intervention date windows, age groups) that pose minimal risk to participants. No PHI will be included in any of the data files received from MassHealth or analyzed by MGH staff and the de-identified data will be protected. Only aggregate results will be presented.

These data will be stored on Partners servers and behind the Partners Information Security firewall. Data will not leave the performance site and will not be stored on removable devices such as laptops or external drives. Access control to the data is maintained centrally via Active Directory, and will not be accessible to persons outside of the study team (access is by username and password authentication).

Request for Waiver of Written Consent

1) **The proposed research involves no more than minimal risk to participants**.
   We propose to study the effects of enhancements to a system of usual care delivery on primary care provision of evidence-based 'standard of care' treatment for tobacco

addiction and smoking cessation rates. Patient safety will be overseen by primary care providers and the psychiatric rehabilitation team in the course of usual care.

Participants will be asked to respond to a brief 5-minute survey once a year for 3 years and may be offered CHW support as a supplement to their usual psychiatric rehabilitation supports, which they can either accept or decline, as they do for other psychiatric rehabilitation services, such as housing support and vocational support. Whether a person agrees to participate or not, their primary care clinic staff may receive academic detailing regarding safety and efficacy of standard of care smoking cessation treatment for people with psychiatric illness.

In addition, the burden to participants is minimal. In this pragmatic trial, the interview questions are indistinguishable from standard self-reported health assessment questions typically asked during this meeting with the psychiatric rehabilitation team, for example how much they typically smoke in one week, the SF-1 question: How would you rate your overall health? Excellent, Very Good, Good, Fair, or Poor, and questions about their routine preventative primary care to do with smoking cessation treatment. No PHI will be collected.

We propose to disclose to MassHealth the MassHealth IDs of patients participating in the study and the date range for the interventions being evaluated (AD and AD+ CHW), and a limited set of study data in order to obtain de-identified claims data to assess the impact of the intervention on medication use and abstinence. Of note, MassHealth has detailed information on patients' diagnoses (including mental health diagnoses) from medical claims and their service providers, thus we would not be disclosing new information on SMI diagnoses of participants to MassHealth. The primary information that MassHealth would learn through these disclosures are whether and when enrollees or their PCPs participated in this smoking cessation trial of AD with or without CHW support and their abstinence status during the three study years. This is not information of a sensitive nature, and MassHealth has privacy protocols to protect such information. Use of these data will be governed by a Data Use Agreement.

MassHealth will disclose deidentified data on smoking cessation medication claims during the study period for study participants with MassHealth. These claims data will be scrubbed of all 18 HIPAA identifiers and derivatives, including dates of service and MassHealth IDs. Claims will only be identified using a new encrypted ID generated by MassHealth. Linkages with survey-collected data elements will be limited to the minimum required for the analysis, those that pose minimal risk of identification and individual and combined data elements will be required to have cell sizes of at least 10 people, per standard data suppression guidelines.

The primary risk of the disclosure of MassHealth smoking cessation claims to the study team is whether participants filled smoking cessation medication prescriptions during the study period and potential loss of confidentiality to study participants of participation in a services implementation study to MassHealth. However, we consider the risk of such loss of confidentiality to be minimal since data will be deidentified and transferred and stored securely; moreover, the study team members analyzing the claims data will not have any direct contact with participants or even with study staff who provided the study intervention.

In summary, we consider the risks of the use and disclosures of the data required for the pharmacy claims data to be minimal given the relatively high prevalence of smoking in this study population and because the interventions being tested (academic detailing and CHW support) do not carry stigma, are well-integrated into care, are randomly assigned, and will not affect MassHealth benefits in any way. In addition, study staff receiving claims data from MassHealth will only receive deidentified data without PHI, all data will be transferred using secure methods and stored on secure, password protected servers with no access to outside individuals.

2) **The waiver or alteration will not adversely affect the rights and welfare of the subjects.**

The waiver of written consent will not adversely impact a person's access to or the nature of their ongoing psychiatric rehabilitation services or primary care in any way nor adversely affect their rights or welfare. A brief verbal consent process outlined below is designed to protect the rights and welfare of subjects as they decide whether to participate in the brief annual survey.

Patients will be asked by their psychiatric rehabilitation staff if they may be willing to complete the brief study survey during their annual psychiatric rehabilitation meeting. For those who agree, a research coordinator will use a script at this meeting to explain the purpose of the survey, confirm that a participant understands what participation entails and that participation is voluntary, provide an opportunity to ask questions and an opportunity to refuse participation. An identical process will be followed in study year two when the CHWs offer to work with patients who are randomly assigned to be offered this support.

Thus, a waiver of written consent to participate will not adversely affect the rights and welfare of participants. Independent of whether a potential participant agrees to respond in the 3 annual surveys, they may benefit from the academic detailing that may be provided to their primary care clinic staff.

3) **The research could not practicably be carried out without the waiver or alteration**.

This study could not be practicably carried out in the geographically extensive and often chaotic community psychiatric rehabilitation system setting without a waiver of written consent and alternate use of verbal consent to participate in the annual survey because of the pragmatic nature of the study setting. This study proposes a pragmatic approach in which information will be collected as part of the normal course of an annual psychiatric rehabilitation visit, held in the community. We will have 4 full time research coordinators aiming to meet, at some place in the community (their group home, supported apartment, day program) for approximately 5 minutes per year with up to 1300 people.

The psychiatric rehabilitation agencies who administer these services have communicated that obtaining written consent for this research involving no more than minimal risk is not practical in this setting. Specifically, obtaining written consent would significantly increase the time requirement for this brief survey, which is designed to be given in the pragmatic usual care setting of the annual psychiatric rehabilitation team meeting. In our experience, the consent process generally takes 30-

45 minutes in this population, which is the usual length of the entire annual psychiatric rehabilitation meeting, while this brief survey should take 5 minutes or less in most participants. Requiring written consent would thus dramatically increase participant burden and make the conduct of the survey during the psychiatric rehabilitation team meeting, which usually takes only 30 minutes, unfeasible because of staff time, space constraints, and participant tolerance of the process. At the least, requirement of written consent would reduce enrollment and compromise the representativeness of the sample. It is more likely that requirement of written consent for the brief annual survey would make data collection during psychiatric rehabilitation annual visits, and thus the pragmatic design to study the impact of a service intervention on an entire system of care, not feasible. It is for these reasons also that a requirement that study staff make in person contact with each potential participant twice, first for consent and second, at least one day later, to conduct the survey would also make the study unfeasible. Thus we propose that the study coordinator obtain verbal consent at the same meeting in which they will conduct the baseline survey.

The analysis of claims data on prescribing and use of smoking cessation medication treatment would not be possible if consent was required of all participants for access to their doctor's de-identified prescribing data. The study has enrolled 1166 participants. It is important to be able to utilize de-identified prescribing data for as many participants as possible in order to compare administrative measures (i.e., not based on self-report) of medication use across the study intervention arms to assess the effectiveness of the interventions on prescribing and the effects of medication use in this understudied population on abstinence. The funder specifically asked for these data to be included in the study, but made the request after the initial protocol was already implemented. The majority of withdrawn participants have lost agency services and would be extremely difficult to locate for consenting purposes. For participants we are able to contact, requiring consent to obtain and use de-identified pharmacy data would impose a significant participant burden. It would take approximately 30 minutes, a substantial amount of time, to explain the processes for disclosing and deidentifying the data and why this represents minimal risk.

4) **Participants will be provided with additional pertinent information after participation.**

At the initial meeting with the study coordinator, during the verbal consent process, participants will be provided with a fact-sheet that details important information about the study, including who can be contacted for more information. Participants will also be offered a copy of the Privacy Notice.

5) **The research involves no more than minimal risk to the privacy of the participants**.

This research involves no more than minimal risk to the privacy of participants. No PHI will be collected by MGH study staff. Please see above for the plan to protect identifying information from improper use and disclosure.

The use of pharmacy data involves no more than minimal risk to participants. All PHI disclosed to MassHealth will be protected using secure transfer and storage and we will disclose the minimum amount of data necessary (e.g., IDs, intervention date windows, age groups) that pose minimal risk to participants. No PHI will be included in any of the data files received from MassHealth or analyzed by MGH staff and the de-identified data will be protected (details above).

Only aggregate results across groups of providers or patients will be analyzed and shared; no information on individual providers or patients will be generated or shared. We will not publish or report any cell size with 10 or fewer participants in accordance with data suppression policies.

V. STUDY PROCEDURES

This study aims to compare the effects of service interventions, AD+CHW, AD, CHW and TAU, on smoking outcomes in a large community psychiatric rehabilitation system of care.

Allocation concealment: Intervention allocation will be randomly assigned by computer generated list.

Blinding: Neither participants nor providers will be blind to the intervention assigned. Research coordinators who conduct the surveys with all participants will be blind to intervention assignment to the extent possible as the participant may volunteer information that makes study assignment clear to the coordinator.

1. Overview of Survey Visits:

Research assistants will attend the annual, scheduled CBFS and ACT rehabilitation team treatment planning meeting in the community to conduct an annual survey when the psychiatric rehabilitation team is engaging with the patient. The schedule of psychiatric rehabilitation team meeting is fixed according to the month of enrollment in CBFS or ACT, and the study assessments will accommodate this schedule. The brief annual survey will take 5 minutes for most participants. Those who complete the baseline survey will be asked to repeat the survey at their next two annual psychiatric rehabilitation team meetings.

2. Survey Items

2.1 ***Demographics***: age, sex, race, living situation (Group Home/Supervised Housing or Independent Living) (Baseline Assessment only)

2.2 ***Smoking Status:*** If smoking: number of cigarettes smoked per day; if prior smoker: time since last cigarette and quitting method.

2.3 ***Smoking cessation services in the past year:*** If smoking: report of whether smoking status was assessed by their primary care physician or nurse, whether advice to quit smoking was given, whether prescription of pharmacotherapeutic cessation aids and/or referral to behavioral smoking cessation treatment were offered or made.

- If pharmacotherapeutic cessation aids were prescribed, we will ask if the was filled, and, if so, whether the medication was used, and, if so, for how long.

- If behavioral smoking cessation support was recommended, we will ask if this support was used and, if so, what type (quit line, smoking cessation group or individual treatment) and how many sessions were attended.

2.4 If smoking: ***The Heaviness of Smoking Index*** (HSI) will be administered. It consists of 2 questions: time to first cigarette of the day and number of cigarettes smoked per day. The HSI and its individual items are strong predictors of quitting behavior, now validated in the International Tobacco Control cohort with 8,000 respondents/wave and 6,000 for prediction of cessation outcomes [75].

2.5 ***Health related quality of life***: The single item self-reported general health status question (SF-1) is well validated as a descriptor of individual health and wellbeing as well as community health status. [76] SF-1 scores are highly correlated with measures such as future health care use, mortality, disability, and mental health status [77-82] and SF-1 scores are significant indicators of health outcomes, independent of gender or racial/ethnic group. [78]

2.6 In those who report having quit smoking: Carbon monoxide in expired air, ***Expired CO,*** will be measured with a small, hand-held CO monitor. To do so, participants will blow into a straw attached to the device, a Bedfont Smokerlyzer II (Kent, England), following a 15-second breath hold to verify self-report of non-smoking status. Expired CO <5 parts per million (ppm) is consistent with smoking abstinence.

- We will measure cotinine in saliva in those whose expired CO is >5 ppm but report smoking zero cigarettes per day in the past 7 days and are not using nicotine replacement therapy. To do this, participants will provide a saliva sample via passive drool that will be tested with a NicAlert® dipstick (Nymox Corp., Hasbrouck Heights, NJ). The NicAlert® test displays seven zones that represent a range of cotinine levels from 0 (0–10 ng/ml) to 6 (> 1000 ng/ml). Participants that obtain a level between 1 (10-30 ng/ml) and 6 will be considered to be smoking

This is standard for biochemically verified abstinence and a critical component to obtaining reliable estimates of smoking status, the study's primary outcome, which will be used to judge the utility of the interventions being tested.

3. <u>Interventions</u>

As part of their ongoing care, staff in CBFS and ACT psychiatric rehabilitation programs identify those in their programs who regularly smoke tobacco and the clinics providing their medical care. In cohort 1, clinics were randomized to receive AD to their clinicians or TAU. Participants whose primary care practices were assigned to receive AD were randomized to be offered a CHW (AD+CHW) or not (AD). In cohort 2, participants were randomized to receive CHW support or TAU These interventions are detailed below.

There will be no prescription of or distribution of any smoking cessation medication of any kind to study participants by study staff. Any prescription of or recommendation for smoking cessation medication will be done in the clinical setting by clinical treaters.

3.1. Usual care (TAU) for adults with SMI in Massachusetts consists of rehabilitation services publicly funded by the state and traditional fee for service outpatient medical and psychiatric care. Importantly, medical care is not programmatically integrated with the psychiatric rehabilitation services. Patients who receive CBFS or ACT psychiatric rehabilitation

services from the primary agencies delivering such care in the Boston area, who agree to enroll in the study and whose primary medical clinic is assigned to the TAU arm of the study will meet with a RA at three consecutive, regularly-scheduled, annual psychiatric rehabilitation team meetings for brief survey. They will receive no other study-related intervention.

3.2. Academic detailing (AD) is a targeted continuing medical education (CME) strategy that adapts social marketing techniques, using mixed interactive and didactic formats in individual and group settings integrated into the practice setting to promote beneficial changes in medical care [83]. AD helps clinicians understand and adopt targeted evidence-based practices and is one of the few Continuing Medical Education (CME) interventions that has consistently demonstrated improved alignment of physician prescribing behavior with evidence-based practice [84-86]. AD has been effective specifically in increasing provision of smoking cessation treatment in the general population and in low-income, disadvantaged areas [87-90] and to improve medication treatment for those with SMI [91]. Evidence strongly indicates that physician advice to quit, prescription of pharmacotherapeutic cessation aids, and referral for behavioral smoking cessation treatment is highly effective for smoking cessation in those with SMI. Local experts will provide structured alternatives needed to overcome strongly held but incorrect beliefs of prescribers. Brief reinforcement visits will increase success rates. AD will allow a clinical educator to engage with a prescriber, understand their practice patterns, assess their needs, and identify gaps in knowledge, and then offer specific, action-oriented recommendations to improve the quality of care.

Each prescriber working in clinics assigned to the AD intervention will be invited to a one-hour staff meeting (30-minute AD lecture and 30 minute interactive question and answer period) at which local experts, the academic detailers, will present the strong evidence base for smoking cessation treatment in those with SMI to clinic staff. Prescribers will be eligible for one hour of free Continuing Education Units (CEU) for attendance at this regularly scheduled staff meeting. To receive CEU credits, prescribers who attend this meeting will be asked to report how frequently they recommend smoking cessation treatment to their patients with SMI, to complete an evaluation of the AD session, and to rate how likely they are to increase implementation of tobacco dependence treatment to those with SMI as a result of the first AD visit (Exploratory Aim 1). This initial group AD meeting will be followed by 1 on 1 academic detailing visits with prescribers who agree that will consist of 5-10 minute targeted individual sessions with prescribers. Prescribers will be offered up to two AD visits per year for two years. Drs. Evins, Reyering, Thorndike and an internal medicine fellow from the National Resource Center for Academic Detailing (NaRCAD) (http://www.narcad.org) at the Brigham and Women's Hospital will provide AD to prescribers at the 20-30 primary care clinics that are assigned to the AD intervention to promote implementation of evidence-based pharmacotherapeutic and behavioral smoking cessation treatment for smokers with SMI.

Evidence to be presented to prescribers by AD: AD will present the compelling evidence for efficacy and tolerability of pharmacotherapeutic cessation aids combined with behavioral treatment for smoking cessation for those with SMI [92] along with strong and growing evidence that smoking cessation is associated with improved psychiatric symptoms such as anxiety and depression [93]. The academic detailing content will focus on:

i) The United States Preventive Services Task Force (USPSTF) recommendation, with Grade 'A' evidence, that clinicians ask all adults about tobacco use and provide cessation interventions for those who use tobacco products.

ii) The strong evidence base for safety and tolerability of nicotine dependence treatment, specifically for smokers with SMI,
iii) Specific information critical to safe and effective provision of smoking cessation treatment in conjunction with the multiple other medications commonly used by those with SMI,
iv) Tools to improve effective communication with individuals with SMI.

AD will present robust evidence for efficacy for bupropion alone and in combination with nicotine replacement therapy (NRT) and the strong and growing evidence for safety and efficacy of varenicline for smoking cessation specifically in those with SMI that has emerged since the PORT Guidelines were published in 2010. AD will emphasize that, like smokers in the general population, efficacy of pharmacotherapy is enhanced by behavioral treatment, but unlike the general population, behavioral treatment alone is associated with a very low average cessation rate of 4%. AD will educate prescribers about abnormalities in brain nicotine receptors in those with schizophrenia spectrum disorders [94-96], that may confer a particular cognitive benefit from nicotine [97-100], and medications that substitute the actions of nicotine in the brain, such as NRT, bupropion [41], NRT [97, 98] and varenicline [101-103] to improve cognitive impairments associated with schizophrenia and maintain abstinence [103-106].

3.3. Community Health Worker (CHW) The CHW will offer to support patients and prescribers in health promotion and preventive care in general and specifically to support communication between the primary care provider and patient regarding smoking status, smoking cessation, and to aid implementation of any smoking cessation treatments recommended by prescribers. CHWs will complete the standard CHW certificate training program in general preventive medicine, available through the Boston Public Health Commission: www.umassmed.edu/ahec/. CHWs will then receive the following training:

i) Evidence based, health empowerment training designed for peer specialists to improve health literacy, healthcare decision-making, and support a positive alliance with those with SMI and their prescribers. These person-centered health empowerment trainings include: a. Whole Health Action Management (WHAM), a SAMHSA-HRSA Center for Integrated Health Solutions training program funded in Massachusetts by the DMH in partnership with the Transformation Center [107] to encourage increased resiliency, wellness, and self-management of health and behavioral health among people with mental illnesses and substance use disorders [108, 109]
ii) CHWs will complete the 2-day, accredited Tobacco Treatment Specialist (TTS) certificate program from University of Massachusetts designed for health care professionals and paraprofessionals [110].
iii) Training with Drs. Reyering, Evins and Thorndike on the content of the AD materials being delivered to prescribers.
iv) Orientation to the CBFS and ACT programs of psychiatric rehabilitation.
v) Training with Drs. Cather and Pachas on cognitive behavioral smoking cessation treatment for those with SMI [25, 26, 37, 111-113].

CHWs will receive weekly group supervision with supervisors and monthly group supervision with senior clinical staff to review cases, as we have done successfully in prior large intervention evaluation research projects and as is routine in the CBFS and ACT practice model. As requested by participants, each CHW will provide flexible individual support to up to 35 participants and their prescribers as follows:

a. Partner with patients to identify their smoking-specific health goals as part of their recovery plan, using techniques emphasized in their training on tobacco treatment and health empowerment.

b. Provide practical preparation and support for prescriber visits, including making appointments, arranging transportation, helping patients to compile an accurate medication list to bring to appointments.

c. Provide practical assistance to patients to communicate their smoking behavior and stage of change to their prescriber and assist them in understanding the treatment options recommended by prescribers.

d. Assist patients in obtaining recommended treatment through support obtaining prescriptions, liaison with staff who aid medication administration, and transport to smoking cessation groups.

e. Promote communication of cessation attempts between prescribers and caregivers in the extended system of rehabilitation care in those who begin pharmacotherapies, to improve support for the cessation effort and broad monitoring and communication of any medication side effects, nicotine withdrawal symptoms and psychiatric symptom

f. Co-lead smoking cessation groups with clinical staff with manualized content tailored to people with SMI, delivered in the psychiatric rehabilitation settings in which the individuals are served, including club houses and wellness centers. Fidelity to the CBT manual and clinical technique will be measured with a quantitative scale developed for this purpose and extensively used by our group.

4. Mixed Methods

4.1 Quantitative Data Review

To inform the qualitative data collection, we will use quantitative data to characterize performance levels, and engagement level, that will then frame our purposive sampling to recruit a representative sample at various stakeholder levels. Purposive sampling involves the intentional selection of participants based on pre-selected criteria that relates to the research questions of interest (i.e. barriers and facilitators). We will review and retrieve existing quantitative data.

4.2 Consent Process

Informed consent will be obtained prior to the collection of any data for the study. Study staff will discuss the study in detail with the participant. Information about the study and its purpose, including potential risks and benefits will be provided in written form in language understandable to the participant. Participants will be given the opportunity to ask questions, and it will be explained that even after they have made a voluntary agreement to participate in the study, they may withdraw from the study at any time without penalty. For smokers with SMI, study staff will evaluate the participant and assess his or her competence to provide informed consent and this or her factual understanding of the study and its risks using a Consent Form Test. This questionnaire consists of 5 true-false questions about important aspects of the study procedures, potential risks, and the patient's right to end participation at any time. A participant must score 80% to participate. If the participant is deemed not competent to consent to study procedures due to illness or any other reason, they will not be included in this part of the study. In general, subjects who provide informed consent will be given a copy of the signed consent form to keep.

4.3 Qualitative Data Collection

We will collect demographic information (age, sex, ethnicity and race) for all subjects not previously enrolled in the annual survey portion of the study. In order to collect data relevant to the CFIR constructs, we will conduct semi-structured individual interviews with the purposefully selected participant stakeholders. Semi-structured interviews will be audio-recorded for transcription and analyzed iteratively. The CFIR constructs will guide the development of the questions for the interviews and will likely include semi-structured questions similar to the following "I know that in your work as a CHW you've likely had a wide variety of experiences working with clients with varying rates of engagement in the program and cessation.

Please think about one of the clients you have been working with for awhile. Please tell me a about the social situation of this client, and then, in as much detail as you can, starting from the beginning, tell me about your experience guiding and supporting the client in the program.
[Who else (doctors, family members, friends, group home staff) was involved?]
[What happened next?]
[Why do you think that happened?
[How did you tailor to specific client needs?]
[What went well? Challenges?]

How is this a typical experience, and what have kinds of variations have you seen?
[Probes: Good variations, bad variations, surprises, program dropouts]

and

On this project, our team feels as though CHWs have been a key to success. So with your own experience becoming and working as a CHW, what in your mind would be critical for successfully using this program elsewhere?

Probes

[What about the?
-your own personal qualities?
-the training program?
-equipment to implement the program?
-clinical support/supervision?
-camaraderie among CHWs?]

Are there any gaps in the program that you think would be necessary?"

The systematic qualitative data collection of different levels of participants is crucial due to the distinct roles of the participants in patients' care, their different perspectives on barriers and facilitators of integrating interventions in primary care settings, and the differential ability to impact current and future change at the organizational and public health policy level.

The data collection and analysis will proceed iteratively with several interviews for each level. Iterative data collection and analysis will proceed until we achieve data saturation, within and

across levels, the point when no substantively no information is being elucidated.

4.4 Participant Stakeholder Samples

The following participant samples will be used for collecting qualitative data:

a) Patients:

Interviews with 30-45 patient participants lasting 30-45 minutes will be conducted. 10-15 interviews each for patients with low/no, moderate, and high engagement, each evenly divided by those with low and high levels of behavior change, yielding a total of 30-45 interviews or until thematic saturation is reached. For each of the stratification groups, patients with differing levels of engagement (e.g., low/no, moderate, high) with the intervention will be recruited to maximize representativeness. We will compensate participant smokers with serious mental illness with $15 for their participation in the qualitative interview.

b) Providers/PCPs: We will conduct semi-structured individual interviews each lasting approximately 30 minutes, with 10-15 interviews anticipated for each level of engagement with the AD intervention (e.g., low, moderate, high), each evenly divided by those with low and high degree of behavior change (provision of evidence based smoking cessation treatment to their patients with SMI who smoke) yielding a total of 30-45 PCPs.

In order to further understand the impact of the CHW on the triad relationship, we will ask PCPs to discuss their experiences working with patient participants assigned to CHWs and patient participants without a CHW, as many PCPs treat patient participants assigned to CHW and no CHW arms. We will compensate providers/PCPs with $15 as a prepaid incentive for their participation in the qualitative interview.

c) Community Health Workers (CHWs): All 12 CHWs interviewed using semi-structured individual interviews, including one CHW who left the study at the start of Year 2. Interviews will last approximately 30-45 minutes. CHW group stratification will be based on intervention intensity and fidelity averaged over caseload. We will compensate CHWs with $15 for their participation in the qualitative interview.

d) Leadership of Clinical Service Organizations: We will conduct a total of 12-16 individual interviews lasting 30-45 minutes. We plan to conduct interviews with 6-8 members of the leadership of the recruited human service organizations and 6-8 members of leadership from PCP clinics, including the medical directors, CEO(s), and other leadership team members. We will compensate leadership of clinical service organizations with $15 for their participation in the qualitative interview.

e) Payor and Policy Leadership: We will conduct a total of 14-18 individual interviews lasting 30-45 minutes with payer /policy leadership members. We plan to conduct interviews with 7-9 members of leadership from payors including Medicaid, accountable care organizations and contractors of service (e.g. Department of Mental Health), as well conduct interviews with 7-9 members of policy leadership, including state executive and legislative branch officials. We will compensate payor and policy leadership with $15 for their participation in the qualitative interview.

4.5 Mixed Methods Research Questions

MRQ 1a. Among patient participant, CHW and primary care provider (PCP) stakeholders, what are the barriers and facilitators to use of the intervention and how do these compare according to performance level, namely, patient quitters, PCP prescribers, and CHW facilitators?

MRQ 1b. Among patient participant, PCP, and CHW stakeholders, what are the barriers and facilitators to use of the intervention and how do these compare according to level of engagement?

MRQ 2a. How do the PCPs, grouped by primary care clinic, differ by performance level and how do their experiences with the intervention, and the barriers and facilitators compare across these groups?

MRQ 2b. What is the association between engagement with the AD intervention among high or low performers, and how did barriers and facilitators experience compare across these groups?

QQ (Qualitative Question) 3. What barriers and facilitators do stakeholders, such as clinical, payor and policy leaders anticipate impacting the implementation of the integrated smoking cessation treatment?

Time and Events Table

VII. BIOSTATISTICAL ANALYSIS

1. Analytic Plan.

With the original 3-arm design, 1/3 of clinics that serve 3 or more smokers with SMI will be randomly assigned to the TAU arm and 2/3 will be assigned to receive AD. At the clinics assigned to AD, half of the smokers with CBFS or ACT services who participated in the baseline assessment will be randomly assigned to be offered CHW support to quit smoking. The primary outcome measure will be the difference in smoking rates and self-reported overall health from year 1 to year 3 between those assigned to AD+CHW compared to TAU. In secondary analyses, we will also compare these outcomes in the AD+CHW group compared to the AD group, and in

Year	1	R	2	3
Study Visit	1	A	2	3
Questions		N		
Demographics (age, sex, race, living situation)	X	D		
Smoking Status	X	O	X	X
Heaviness of Smoking Index (HSI)	X	M	X	X
Smoking questionnaire	X	I	X	X
Single item Health related quality of life (SF-1)	X	Z	X	X
		A		
Biomeasure		T		
Exhaled CO (in those who report being non-smokers)	X	I	X	X
		O		
Quantitative Data Collection				X
Payment	$5	N	$5	$5

AD compared to TAU. For participants who receive primary care from a clinic that serves two or fewer adult smokers with SMI, we will randomize half to receive CHW services. This comparison can be kept entirely separate from the main analysis of AD vs AD+CHW vs TAU

To include participants from Cohort 2, we conducted a secondary, factorial analysis of the impact of the two interventions and their combination, using cohort as a factor, that was planned when we randomized participants whose clinics cared for ≤2 participants.

To determine the influence of the assigned intervention mediated via its impact on TUD medication use, and varenicline use specifically, the unmediated impact of the study interventions on abstinence, and the impact of TUD medication use and varenicline use specifically on abstinence we conducted mediation analyses using the combined cohorts. We assessed associations between intervention assignment, TUD medication use, and year-2 abstinence via path analyses based on logistic regression. Separate analyses assessed the impact of taking any TUD medication and varenicline specifically. Estimates of the indirect effect were computed per each imputation run and pooled using Rubin's method.

2. Statistical methods.

Aim 1. Hypothesis 1a. *Those who receive* AD+CHW *will demonstrate higher rates of biochemically verified tobacco abstinence than those who receive usual care (TAU).* The primary outcome will be the proportion of smokers who are abstinent at their Year Three Assessment. This will be 12-24 months after randomization to study interventions because assessments are conducted in the pragmatic setting of the annual psychiatric rehabilitation team meetings. This smoking abstinence rate will be compared between the two groups using a generalized linear mixed models logistic regression, with random effect for clinic, assumed to be normally distributed [114]. **Hypothesis 1b.** *Those who receive AD+CHW will demonstrate higher rates of biochemically verified tobacco abstinence than those who receive AD only*. This rate will be compared between the two groups using logistic regression. **Hypothesis 1c.** *Those who receive AD will demonstrate higher rates of biochemically verified tobacco abstinence than those received TAU.* This rate will be compared between the two groups using generalized linear mixed models logistic regression. Hypothesis 1d. Participants assigned to receive CHW will demonstrate a higher rates of biochemically verified, 7-day point-prevalence tobacco abstinence than those assigned to TAU at the Year 3 Assessment. This will be tested with factorial analysis in the combined sample, using cohort as a factor. Additionally, we will compare MassHealth pharmacy claims data for smoking cessation medications (varenicline, bupropion and nicotine replacement therapy) to examine differences in prescribing patterns of providers randomized to AD compared to those randomized to TAU. We will also examine the effect of the interventions on rates of participants filling prescriptions for smoking cessation medication (i.e. AD, AD+CHW, CHW, TAU)

Aim 2: Hypothesis 2. *Those who receive* AD+CHW *will demonstrate improved Quality of Life compared to those who receive usual care, as assessed with the SF-1 (Overall Health).* We will assess this hypothesis with a random effects model with baseline, duration of follow up, and treatment group as covariates and a clinic random effect. We will use data from the last visit during the study as the dependent measure.

Exploratory Aim 3: Through data collected by the RAs for both AD+CHW and TAU groups, we will identify differences in care processes that will be suggestive of specific mechanisms. The main components of the intervention are i) AD to prescribers, which is designed to increase the number of smoking cessation interventions initiated including prescriptions written and referrals for behavioral treatment; and ii) the availability of CHW

support to patients and providers, which is intended to improve client engagement with prescriber recommended tobacco treatment, including increasing access to, and use of tobacco treatment pharmacotherapies and attendance at behavioral smoking cessation treatment. The CHW, through encouraging cessation attempts and through client support, is expected to increase the effectiveness of the pharmacotherapies and behavioral groups, and reduce relapse risk. We will conduct exploratory analyses examining differences in self reported prescriptions received, prescriptions filled, and smoking cessation groups attended by study arm using linear mixed effects models with clinic random effects.

Exploratory Aim 4. Hypothesis 4a: *Participants with schizophrenia and schizoaffective diagnoses will demonstrate lower absolute rates of biochemically-verified, 7-day point-prevalence tobacco abstinence than those with other diagnoses.* This rate will be compared between the two groups using generalized linear mixed models logistic regression. **Hypothesis 4b**. *Participants with schizophrenia and schizoaffective diagnoses will a demonstrate larger effect of treatment (AD+CHW) vs no treatment (TAU).* This effect will be compared between the two groups using generalized linear mixed models logistic regression. These hypotheses are underpowered to detect an effect and are considered to be exploratory only.

Aim 5: We will use an interactive convergent design, as the emerging qualitative and quantitative data findings will inform respectively additional analyses. Our interactive intramethod approach or "iterative approach" will allow for us to generate hypotheses resulting from the qualitative data analysis which we will examine quantitatively using Year 3 data to further inform the joint display analysis.

Quantitative Data Analysis

Using existing data, we will conduct quantitative analyses appropriate to establish cut-off levels for 3-level categorical measures of engagement and performance. As described above, these levels of performance and engagement will be used for purposive sampling for qualitative interviews. We also anticipate conducting additional quantitative data analysis when we test any hypotheses generated from the results of the qualitative data analysis.

Qualitative Data Analysis

All individual interviews will be audio-recorded, transcribed verbatim, cleaned, and entered into NVivo 12 software program for data management and analysis. All data will be checked for accuracy. We will document our analysis process, recording all coding decisions for further review. All analyses will follow procedures to ensure reliable qualitative data analysis, including establishment and training of coding team, ongoing recalibration meetings to ensure reliability of coding team, and training and ongoing recalibration to reduce the potential of biasing in coding. Rater agreement will be assessed through a second rater coding a subset of the data until a high level of reliability (Kappa ≥ 0.80) is established. Weekly consensus meetings will resolve disagreements.

We will use a theory-driven approach in which we will explore the relationship between the findings and the CFIR framework. The goals, objectives and key research questions will guide all aspects of the qualitative analyses. Using content analysis, we will identify analytical categories to describe and explain our observations. Our work will occur in five stages outlined in Mays et. al (2004)'s framework approach to qualitative analysis: 1) Familiarization, 2)

Identifying a Thematic Framework, 3) Indexing, 4) Charting, and 5) Mapping and Interpretation. In the second stage, codes will be derived deductively by identifying categories at the beginning of the research (e.g., elements of the CFIR framework) and inductively by identifying those that emerge gradually from the data. We will use operational definitions of each code. Using constant comparison, we will update the coding model as our efforts to index the data lead us to further refinement. In the charting and mapping phases, we will integrate quantitative and qualitative data for purposes of convergence, contextualization, and expansion. Based on our research questions, we will identify themes and look for the commonalities and variations in the different participants' perspectives of the barriers and facilitators in integrating evidence-based treatments in routine clinical care. The data integration will facilitate a more fine-grained understanding of processes and characteristics that influence future scale-up and dissemination initiatives.

Mixed Methods Analysis

We will conduct a Joint Displays Analysis in which quantitative and qualitative concepts will be matched and displayed on a single matrix in order to allow for meta-inferences to be drawn on outcomes of interest, namely the barriers and facilitators to effective implementation of the intervention components with smokers with SMI served in primary care settings. These can be constructed for each MRQ and by level. The ultimate goal is to develop metainferences, that is, interpretations based on both types of the mixed data. This approach facilitates learning a greater whole than a sum of the individual parts

3. Power analysis and sample size determination.

Power Analysis: With a 3-arm trial, we retain excellent power to test the initial primary hypothesis that AD+CHW is superior to TAU, and can test in exploratory analyses the effects of the components of the AD+CHW intervention. We have confidence that the abstinence rate with TAU will be in the range of 3-5% or lower, based on the 4% placebo abstinence rate in RCTs of pharmacotherapy and behavioral smoking cessation treatment for those with SMI, and that the AD+CHW arm abstinence rate will be between 16%-18%.

We are unsure of the effect the academic detailing (AD) intervention alone will have on abstinence rates. AD could inspire quit rates as low as 3-7%. Or AD may be nearly as effective as the combined effect of AD+CHW, with abstinence rates as high as 14-20%. Or the abstinence rates among those whose treaters receive AD without CHW support may lie somewhere in between, in the 9-10% range. Bearing these features in mind, we present the following tables with power estimations based on 1000 simulations, where T=TAU, A=AD and C=AD+CHW:

Table 1. Optimistic TAU, pessimistic AD + CHW, and a range of AD effects on abstinence rates:

TAU	AD	AD+CHW	ICC	T vs. A	T vs. C	A vs. C
.05	.07	.16	.03	.14	.96	.94
.05	.095	.16	.03	.51	.98	.67
.05	.14	.16	.03	.95	.99	.10

Table 2. Pessimistic TAU, optimistic AD+CHW, and a range of AD effects on abstinence rates:

TAU	AD	AD+CHW	ICC	T vs. A	T vs. C	A vs. C
.03	.07	.18	.03	.42	.99	.96
.03	.095	.18	.03	.88	.99	.87
.03	.14	.18	.03	.99	.99	.26

4. Sample Size Calculations

Sample size estimate based on hypothesized effect size: We estimated the statistical power of the trial using computer simulation methods. This approach has an advantage over analytic power estimates in that it easily incorporates varying cluster sizes and can employ the exact analysis method contemplated in the planned study. In brief, we simulated the trial 1000 times, including the anticipated effect of the intervention and the eventual data analysis. We repeated this process many times, and the proportion of times we rejected the null hypothesis of no trial effect is our estimated power. We used a conservative approach as follows. We began with a conservative estimate of 40 clinics (we may to enroll up to 60 clinics) in the study and 1100-1170 enrolled patients who are expected to agree to provide baseline data from a pool of approximately 1300 smokers with SMI in the participating rehabilitation programs. Our analysis plan will use information from those who leave the system without data from early termination visits using multiple imputation, but for the purpose of sample size calculation, we assumed no such information, so we use a sample size of 900 patients, which allows for 10-12% to refuse to participate at enrollment and 10-12% attrition per year. While 5% of those served by CBFS have left the system per year over the prior 3 years because they move out of the geographic area, die, do not engage with the rehabilitation team, or are otherwise lost to follow up, we assumed, for the purposes of power calculations, that 10-12% of the patients would leave the study each year. Thus these estimates are conservative.

We then assumed that the proportion of patients who quit smoking in each clinic followed a logistic regression model with a clinic effect that was normally distributed and was different in the intervention groups. The parameters of this model were chosen to give a conservative abstinence rate at the Year Two and Three assessments in the AD+CHW group of 15% and overestimate the expected abstinence rate in the TAU group at 5%. The estimated quit rate in the AD+CHW group of 15% is lower than that observed in clinical trials. It assumes that 65% of the smokers who receive AD+CHW will make a quit attempt and that 30% of those who make an attempt will achieve abstinence [28, 37]. This estimated cessation attempt rate is conservative, as 80% of those queried at MGH Schizophrenia Education Day reported they would make a cessation attempt if aided by their doctor or prescribing nurse. The estimated abstinence rate among those who try to quit is also conservative, as we observed 42% abstinence rates in our recent open label varenicline trial and over 50% abstinence rates in our trial of bupropion plus NRT patch and gum in a similar DMH served SMI population [26, 37]. Further,

we assume that over six months roughly 20% of those who attain abstinence will relapse despite availability of ongoing treatment. [36]

These assumptions are conservative, as 80% of smokers with SMI report that they want to try to quit smoking and would make an attempt if aided by their prescriber, while we assumed 65% would actually try, and we found a 42% cessation rate with 12 weeks varenicline treatment and over 50% abstinence rate with bupropion plus NRT, but assume a 30% cessation rate.

The quit rate of 5% in the usual care group is also conservative, since the average cessation rate across 6 randomized clinical trials summarized in the Tsoi et al Cochrane Review of smoking cessation studies in adults with schizophrenia was 4% at 12 weeks among smokers with SMI who expressed intention to quit smoking within 30 days, set a quit date and received placebo and behavioral smoking cessation treatment. Those in the usual care group are unlikely to receive similarly intensive behavioral smoking cessation treatment [28], further supporting the conservative nature of the estimated 5% quit rate in the usual care group. We used this higher than expected cessation rate for the TAU group in the simulation in order to consider the possibility that publication of the results from our previous work [28, 37, 40] may change clinical practice without the concerted effort proposed under this project, though this has not been observed to date.[3] The variation of the parameter that determined the "clinic effect" was chosen so that the standard deviation of the probability of quitting among different clinics was 9% in the AD+CHW group and 3% in the usual care group. This differential variability reflects the floor effect of the small proportion of quitters in the usual care group, and the variability associated with the intervention in the AD+CHW group. The resulting overall intraclass correlation coefficient of 3% is typical for this type of study [115]. We then used this logistic model to simulate whether each patient would be abstinent at the Year Two assessment.

Our simulation resulted in over 95% power to detect a significant difference in the proportion of patients abstinent at the Year 3 assessment. As a sensitivity analyses, we increased the standard deviation of the parameters governing the variation in the quit rates by a factor of 50%. This would increase the overall intraclass correlation to 7% and reduce the power to 87%. If we considered only patients with schizophrenia spectrum disorders, which is a planned subgroup analysis, we would have 77% of the patients in this subgroup analysis. This would still give 94% power to detect an effect in those with a schizophrenia spectrum disorder.

Missing data

A concerted effort will be made to reach and deliver the academic detailing intervention to all prescribing physicians and healthcare staff at the clinics randomized to the academic detailing intervention. The Academic Detailing staff will make multiple trips to randomized clinics as needed within the first 4 months following clinic randomization. Incentives such as free CEU credits will be offered to encourage physicians and other healthcare staff to participate.

We will attempt to survey all CBFS participants who smoke and receive their psychiatric rehabilitation services through Bay Cove Human Services and Vinfen Corporation. We will attempt to survey all those who agree to participate in the initial survey annually for 3 years. It is a requirement of the Department of Mental Health, who funds the CBFS program, that CBFS participants meet with their rehabilitation teams at least annually, and approximately 97% do so. Self-report of smoking status is routinely collected at this team meeting. We will compensate participants with $5 for completion of the 5-minute data collection. It is hoped that this remuneration will improve participation rates. Approximately 10% of CBFS and ACT participants move out area or terminate services per year. We will not collect subsequent data

from these participants. We will use multiple imputation based on the Year One and Two Assessments to impute the Year Three outcomes for patients who are missing their Year Three Assessment.

VIII. POTENTIAL BENEFITS

1. Potential benefits to participating individuals.

People with SMI die 28 years earlier than those in the general population, primarily due to smoking related illness [15]. It is estimated that half of deaths in those with SMI are due to 1 of 19 diseases identified by the CDC as being causally linked to tobacco use [21]. Smoking cessation by midlife nearly eliminates premature smoking-related mortality [70, 71], and the benefits of quitting are dramatic for all age groups. Smoking cessation treatments are effective but not routinely offered to those with SMI. If this intervention is successful, it can significantly improve smoking cessation rates among the 7.3 million adults with SMI in the US who smoke tobacco [7, 8], and who comprise 13% of all smokers in the US and 2.2% of the total U.S. population [8]. The potential gains in improved health, function, and longevity are high to participants in the study who quit smoking.

2. Potential benefits to society.

This is the first study of its kind to our knowledge to attempt to increase provision of evidence-based tobacco dependence treatment to those with SMI in a large, multi-organization, community behavioral health practice setting and to assess any effect of increased provision of evidence-based smoking cessation treatment on smoking rates and patient-reported health. This intervention has been designed such that, if successful, it could be rapidly implemented within existing systems of psychiatric rehabilitation and primary care, with the goal that it would have a large impact to reduce mortality in those with SMI, the largest lifespan disparity in the US [17, 18].

IX. MONITORING AND QUALITY ASSURANCE

Data and Safety Monitoring Board (DSMB) will meet biannually to assess interim results to determine whether the treatment interventions are associated with substantial risk, when compared with usual care. The board will include a statistician, a primary care provider or internist, and a smoking cessation expert not otherwise associated with the trial. If serious adverse events occur more frequently in the intervention group compared to the usual care group, at a 2-tailed p value of <0.05, then the DSMB will discuss with the Executive Committee whether the trial should be stopped.

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