1. Title

Smoking Cessation After Psychiatric Hospitalization

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3. Purpose

Smoking rates among individuals with psychiatric disorders are disproportionately higher than the general population [1-4]. In fact, these individuals are estimated to consume *almost half* (44.3%) of all cigarettes smoked in the U.S. [5] and have lifespans 25 - 32 years shorter than the general population [6, 7]. In 2011, 1.8 million U.S. adults, including 7.2% of adults with severe mental illness (SMI), received inpatient psychiatric treatment [8]. The majority of psychiatric hospitals ban smoking on hospital grounds, thus providing an opportunity for inpatients to experience abstinence. Yet these patients are infrequently provided with referrals for cessation treatment on discharge (< 1 %) and most resume smoking upon discharge [9]. Moreover, accumulating evidence [10, 11] indicates that smoking cessation may improve psychiatric symptoms in the long run [12-15]. Therefore, the integration of effective cessation interventions within the current mental health treatment system is a public health priority [16]. The overall objective of this project is to adapt a Sustained Care (SusC) model, shown to be effective for medically hospitalized smokers, to smokers with SMI engaged in a psychiatric hospitalization and to test the effects of SusC on smoking cessation and other outcomes relative to Usual Care (UC) for smoking cessation. All patients will receive a 5-10 minute, brief tobacco education session during their hospitalization, delivered by a hospital nurse. If effective, we expect that the adapted, Sustained Care model will be broadly disseminable, may be delivered at a low cost per quit and would have a significant impact in reducing morbidity and mortality due to smoking among individuals with SMI.

Primary Aims: a) In a randomized, pragmatic effectiveness trial [17] designed to assess benefit in real-world practice, we will test the hypothesis that, among smokers in inpatient psychiatric treatment (n = 422), Sustained Care (SusC) will result in superior long- term smoking cessation outcomes compared to Usual Care (UC). We hypothesize that SusC compared to UC will result in significantly higher rates of cotinine-validated, 7-day point prevalence tobacco abstinence at 6- and 12-month follow-ups. b) We hypothesize that a higher proportion of SusC vs. UC patients will use evidence-based smoking cessation treatment (counseling and/or medication) in the month after discharge.

Secondary Aims: a) To quantify the total cost of SusC and UC and, if SusC is effective, assess the incremental cost per quit of SusC compared to UC, b) The SusC intervention will be a cost-effective alternative (incremental cost per quit at 12 months) to UC from health system and individual perspectives. Tertiary Aims: exploratory aims will examine a) the effect of the SusC on health and health care utilization in the 12 months post-discharge (psychiatric symptoms, psychiatric and medical hospital readmissions and emergency room visits), and b) the effectiveness of SusC on smoking abstinence in patient subgroups defined by diagnosis.

4. Procedures

In a randomized, pragmatic effectiveness trial [17] designed to assess benefit in real-world practice, we will test the hypothesis that, among smokers with SMI engaged in inpatient psychiatric treatment (n = 422), Sustained Care (SusC) will result in superior short- and long- term smoking cessation outcomes compared to Usual Care (UC). SusC components include: a) one 40-minute session of in-hospital counseling, delivered by a hospital-employed Social Worker, b) up to 8 weeks of free transdermal nicotine patches, c) Interactive Voice Response (IVR) automated phone calls and text messages, and d) warm transfer to tobacco quitline. All hospital patients will receive a 5-10 minute, brief tobacco education session delivered by a hospital nurse during the course of their hospitalization. Smoking status will be assessed at 1, 3, 6, and 12 months post-discharge (See Figure 1 for study timeline).

The primary outcome is cotinine-validated, 7-day point-prevalence tobacco abstinence at 6- and 12-month follow-up. Additional outcome measures will include the proportion of participants who use smoking cessation medication or counseling after discharge, other tobacco abstinence measures (e.g., sustained abstinence, time to first lapse), and outcomes stratified by patient diagnostic categories. A secondary analysis will examine the incremental cost-effectiveness of SusC relative to UC. Exploratory analyses will examine the effect of SusC on outcomes relative to UC on health and health care utilization including psychiatric symptoms and hospital readmissions and emergency room visits, both psychiatric and medical.

Assignment to Study Condition and Recruitment Feasibility. Once consent has been obtained, participants will complete a baseline assessment (see Measures, below). To preclude possible contamination that might occur if patients within the same psychiatric unit were engaged in both conditions (SusC and UC) concurrently and were to share information with each other, patients within each unit will be recruited and randomized in cohorts of 21, with cohorts being assigned at random to either SusC or UC. Between cohorts there will be a wash out period of no recruitment until all participants from the previous cohort have been discharged (about one week). In order to insure that an equal number of cohorts (and therefore, patients) are assigned to each of the two experimental conditions, this random assignment will be done by choosing from among a fixed pool of cohort entries (20 from each experimental condition). As detailed below, we anticipate recruiting between 10 and 11 participants each month (2-3 per week) during the 40-month recruitment period. In the last two cohorts in each experimental condition, we will recruit one extra patient (22 in all) to achieve our total sample size of 422. Due to concerns about possible experimenter bias, one of our off-site collaborators, who will have no contact with participants, will conduct the random cohort assignment and the research coordinator will be blind to condition assignment.

Intervention Conditions

Sustained Care (SusC) Service Intervention

Sustained Care includes an evidence-based, post-discharge program that is intended to encourage and facilitate smokers' use of continued tobacco treatment (counseling and medication). SusC components include:

In-Hospital Counseling Session. Patients in SusC will receive a 40-minute, in-hospital motivational counseling session about smoking cessation. Seton Shoal Creek social workers, who are otherwise working full-time in total, will provide the SusC in-hospital sessions. These individuals will receive training and ongoing supervision by PI Dr. Brown, who has been a therapist and tobacco cessation intervention researcher for over 25 years and Ms. Jacki Hecht, who is an experienced motivational interviewing (MI) trainer and a member of the Motivational Interviewing Network of Trainers. The social worker/smoking counselors will follow written manuals for SusC in-hospital sessions to ensure standard delivery. Sessions will be audio-recorded in order to insure standardized delivery and to provide ongoing training and supervision when needed. Every effort will be made to assure that the social worker who delivers the smoking intervention is a different individual than the social worker assigned to work with the patient and his/her family regarding their psychiatric issues during the hospitalization. This counseling session is not part of routine hospital care, but rather an intervention that is being developed specifically for this study. The social workers already have training in motivational counseling, which is within the scope of their practice. This counseling session will be based upon the standardized protocol that Dr. Rigotti has implemented for all medical inpatients at Massachusetts General Hospital (MGH), but with modifications for the inpatient psychiatric setting. This counseling session will aim to help patients manage nicotine withdrawal symptoms and provide encouragement and advice to remain quit upon discharge. To alleviate concerns specific to smokers with SMI about the effects of quitting smoking on their psychiatric symptoms, counseling will provide motivational messages and graphical presentation of empirical data indicating that quitting smoking is not likely to exacerbate psychiatric symptoms and in one study, smoking cessation treatment was associated with fewer psychiatric hospital readmissions [18]. We will also attempt to motivate the use of the nicotine patches provided to patients upon discharge (see below). We will use graphical presentation of empirical evidence to highlight the expected benefits of combining behavioral counseling with pharmacotherapy (including the nicotine patch) for smoking cessation, resulting in a 4X greater chance of successfully quitting smoking than quitting on one's own [19, 20]. At the end of this session, the social worker will describe the procedure by which patients will be provided with the nicotine patches upon discharge, IVR telephone or text message counseling, see below). Also, the social worker will obtain a signed release so that a letter can be sent to their outpatient psychiatrist and their primary care physician upon discharge, informing them that the patient is participating in a smoking cessation study and encouraging their support for quitting smoking.

8 Week Supply of Free Nicotine Patches. At time of hospital discharge, the smokers assigned to SusC will receive 4 weeks of transdermal nicotine patches. At the 3rd IVR call or text messaging session (at 2 weeks post-discharge), they will be asked if they are still interested in quitting smoking. If they respond "Yes", they will be asked if they would like to receive 4 more weeks of nicotine patches. If they respond "Yes", 4 weeks of nicotine patches will be mailed to them after contacting them to determine their smoking rate, if smoking. In all cases, the appropriate patch dosage(s) will be provided to them, based upon their pre-hospitalization smoking rate or smoking rate when contacted after the 3rd IVR call or text messaging session. Nicotine patches are an over-the-counter item, have relatively few side effects, and are available locally at pharmacies and other stores. Although the majority of patients will have already been using the nicotine patch during their hospitalization, they will also receive written information on proper medication use and possible side effects. In case of problems in using nicotine patches after discharge, patients will be told to contact the study staff. Study staff will contact a Seton Shoal Creek Hospital psychiatrist, who will follow up with them to address any problems.

Sustained counseling support by telephone for 3 months after hospital discharge. Post-discharge counseling support that persists for at least 1 month was identified in a 2008 meta-analysis as necessary to achieve long-term tobacco abstinence [21]. Patients assigned to SusC will be contacted by telephone 8 times in the 3 months after discharge to receive this level of care. Consistent with our SusC model, two innovations are proposed to improve the disseminability and cost-effectiveness of the intervention:

Interactive Voice Response (IVR), Text Messaging and Free Proactive Telephone Counseling. IVR is a telephone technology in which a computer detects voice and touch tones and responds to callers with prerecorded audio. IVR systems can improve response rates by making multiple calls and doing so outside normal business hours. Colleagues at the Ottawa Heart Institute have adapted IVR technology for providing telephone cessation counseling to smokers after hospital admission for coronary heart disease. We are working with TelASK, the IVR provider used in Dr. Rigotti's research at Massachusetts General Hospital (MGH) and will adapt the model for use in inpatient smokers with SMI. An important innovation here is the opportunity provided to patients for an immediate warm transfer to a registration agent who will offer to connect patients to telephone, web-based and/or text-based quit coaching services. To maximize patients' access to added support for quitting, we will offer to connect patients with quit coaching resources in two ways: 1. by offering to "web enroll" them into the Alere online system that will trigger a quit coach to begin calling them after hospital discharge, and 2. through the IVR system. At the end of the motivational in-patient session, the smoking counselor will ask participants if they are considering quitting smoking within the next 30 days. If the answer is yes, they will ask if the participant would like to gain access to quit coaching resources for additional support. If the participant answers yes to both questions, the counselor will inform the Seton Study Coordinator, who will enroll them into the quit coaching program via the Alere online system. This enrollment will trigger a proactive phone call from a quit coach after the patient is discharged. In addition, the IVR-facilitated system (TelASK Technologies, Ottawa, Canada) will make 8 automated outbound phone calls at fixed times after discharge (2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, and 12 weeks). Each call will collect standard information and offer an immediate "warm transfer" to live telephone counseling services and/or web or text-based quit coaching resources provided by Alere Wellbeing, the quitline provider for 27 U.S. states and more than 650 employers and health insurance providers. If participants accept the warm transfer to the Alere Wellbeing quitline, they will first hear a recorded message letting them know that quitline calls "are routinely recorded for quality assurance purposes". All recorded calls are deleted from the Alere Wellbeing system after 6 months of their occurrence. We are adapting the IVR being evaluated in Dr. Rigotti's ongoing, multisite trial by adding 3 more calls for a total of 8 calls, as well as by adding specific content for smokers with SMI. This will include tailored messages about the effects of smoking on psychiatric symptoms, specifically that smoking cessation is not likely to worsen symptoms and may even result in improved symptoms in the long-term. In addition to being able to receive these messages through IVR, participants will be asked if they are able and willing to receive intervention text messages during the consent process, in the event they are randomized into the Sustained Care condition. For those who agree and are randomized to Sustained Care, TelAsk will send a combination of alternating IVR and text messages to maximize participation in this part of the intervention. This plan affords maximum flexibility, such that participants can engage with the IVR messages at one contact, and text messages at another, and will increase the likelihood that they will engage with this sustained care program.

As in Dr. Rigotti's ongoing study, each IVR call and text messaging session will also assess: (1) current smoking status and intention to quit, (2) current nicotine patch use, (3) nicotine patch side effects, and

(4) patient's desire for quit coaching support. If patients are not using the nicotine patch or other medication as part of their quit smoking attempt, the IVR and text messages will include motivational messages about the importance of using the nicotine patch to assist in quitting smoking.

Criteria to trigger an offer of a transfer to telephone counseling and other quit coaching resources will be: (1) patient's request of counseling; (2) patients who resumed smoking after discharge but still want to quit; (3) patients who never started or who stopped using nicotine patches; (4) patients reporting nicotine patch side effects. Patients transferred to the quitline will receive its standard telephone counseling package with up to 5 proactive calls over 3 months with unlimited inbound calls. The counseling protocol aims (1) to provide cognitive-behavioral smoking cessation and relapse prevention tools, tailored to the individual smoker's characteristics and (2) to provide medication management and adherence support, with the goal of completing a full course of medication. Alere Wellbeing, along with 85% of U.S. quitlines, provides special training for counselors in how to address mental health issues [22] and has a protocol for addressing suicidal ideation reported by callers.

Usual Care (UC)

Patients assigned to the UC condition will receive no other tobacco intervention other than the brief 5-10 minute tobacco education session that all hospitalized smokers will receive, delivered by a Seton Shoal Creek nurse. During this session, they will be provided with written handouts describing the stages of readiness for change in quitting, self-monitoring of smoking, self-management of smoking situations, relapse prevention, managing stress, other quitting tips and use of nicotine replacement therapy.

a. Location

Data collection will occur at Seton Shoal Creek Hospital. This study involves a collaboration between investigators at University of Texas at Austin, Seton Shoal Creek Hospital, Massachusetts General Hospital, Brown University and Butler Hospital in Providence, RI. Investigators at Massachusetts General Hospital, Brown University and Butler Hospital will have no access to participant PHI and will only have access to completely de-identified data. Massachusetts General Hospital, Brown University and Butler Hospital investigators are involved in study design and implementation issues, and in the final year of the study, will be involved in data analysis of study data . . . again, only having access to de-identified data. IVR and text messaging services will be provided by TelAsk, Inc. of Ottowa, Canada and tobacco telephone quitline counseling, web-based and text-based quit coaching resources will be provided by Alere Wellbeing of Seattle, Washington.

b. Resources

This study is supported by a grant from NIMH, 1 R01 MH104562-01.

c. Study Timeline

It is anticipated that participant recruitment and data collection will begin in April 2015. Participants will be recruited over the ensuing 40 months, with recruitment ending July 2018. The last 12 month follow-ups would be completed in July 2019. Six-month follow-up results could be disseminated in the Spring of 2019, and 12 month follow-up results could be disseminated as early as the Fall of 2019.

5. Measures

Overview. All measures will be administered at all timepoints (baseline and follow-ups), with the following exceptions: 1) screening, demographics, smoking history, and nicotine dependence are only collected at baseline; 2) measures of post-hospital smoking cessation treatment use and adherence and the Treatment History Interview are only administered at follow-ups; 3) An In-Hospital Smoking Education and Intervention Questionnaire is only administered at 1-month follow-up. See Table 1 for measures and schedule of administration.

Baseline assessment procedure. All patients will be referred to the study by their attending psychiatrist at Seton Shoal Creek Hospital. Following receipt of a psychiatrist referral into the study, patients' medical records will be screened to collect data relevant to patient inclusion/exclusion criteria. If deemed eligible based upon medical record screen, patients will proceed to participate in the informed consent process (including receipt of the Mini Mental State Exam (MMSE, described below) to assure final eligibility, followed by a baseline assessment conducted by the Research Coordinator. The additional measures will include detailed contact information for the patient and up to 6 close contacts in order to minimize loss to follow-up.

Follow-Up assessment procedure. Outcomes will be assessed 1, 3 and 6 months after hospital discharge. We will also conduct a 12-month follow-up for those participants who report 7-day point prevalence abstinence, confirmed biochemically, at the 6-month follow-up. The 1-month follow-up assesses behavior in the high-risk initial post-discharge period, whereas the 3-month follow-up measures outcomes at the end of SusC counseling and medication treatment. Follow-up assessments include both self-report measures and interview questions. For those participants providing a personal email address, self-report measures will be emailed to them for completion via a weblink to REDCap (see Section 6.d.4. for a complete discussion of REDCap security features). For those participants not providing an email address, paper self-report questionnaires will be mailed to their home or self-report questions will be asked of them over the phone. The Research Coordinator, who is blinded to the participant's group assignment (SusC or UC), will ask the self-report questions over the phone (when necessary) and will conduct the interview portion of the follow-up assessment by telephone. The Research Coordinator will make up to 10 calls at different times of day and days of the week and will call participants alternate contacts when needed to locate them. Participants will be compensated for completing in-hospital and follow-up interviews using ClinCards, a MasterCard product that allows researchers to upload participant payments via a web portal. Participant payments will be in the following amounts: $5 upon hospital discharge for completion of the baseline assessment, $30 at the 1- and 3-month follow-ups and $60 at the 6-month follow-up. We will also conduct a 12-month follow-up for those participants who report 7-day point prevalence abstinence, confirmed biochemically, at the 6-month follow-up. Participants for whom a 12-month follow-up is requested, will be compensated $60 for completion of this follow-up. In addition, those participants who report 7-day point prevalence smoking abstinence at the 6-month follow-up (or 12-month follow-up, if applicable) will be asked to return to Seton Shoal Creek Hospital to provide carbon monoxide and saliva samples for biochemical verification of abstinence, and will be compensated $40 (via ClinCards) for doing so. To maximize follow-up return rates, we will use multiple modalities to schedule phone appointments with participants. During the baseline assessment process, we will ask participants for their permission to send text messages and contact them via Facebook as a way to remind them of their follow-up assessment and to schedule a phone appointment to complete the assessment. A private Facebook Study page will be created that employs the strictest privacy settings. Study staff and participants will only be able to send individual private messages to one another; participants will not be able to post messages or upload information

to the study page profile. In addition, participants will be asked to provide the names, address and phone numbers of up to 3 people whom we can contact to help us locate the participant, if we are unable to reach the participant through the contact information they have provided. If we learn during the follow-up phase of our study that a study participant is currently in jail, we will not continue to contact them for the current follow-up assessment. However, we will continue to call them at future follow-up time points, according to our protocol procedures, to see if the participant is released from jail, able and willing to participate.

TABLE 1 - Measures	Screen	BSL	1MFU	3MFU	6MFU	12MFU
Screening						
Medical Record Review for eligibility	X					
In-Person Screening	X					
MMSE - to assess cognitive capacity for consent	X					
Smoking History; FTND; Withdrawal						
Smoking History		X				
FTND - 6-item		X				
Motivation to Quit Smoking		X				
Thoughts about Abstinence (TAA; 4-item)		X				
Primary Outcome - Smoking Behavior						
Point Prevalence Abstinence (PPA)		X	X	X	X	X
Smoking Cessation Treatment Use and Adherence			X	X	X	X
Bio-Verification						
Carbon Monoxide (CO)					X	X
Saliva Cotinine					X	X
Psychiatric Symptoms						
PROMIS – Depression Short Form 8a		X	X	X	X	
PROMIS – Anxiety Short Form 8a		X	X	X	X	
BASIS 24 – Psychosis Subscale		X	X	X	X	
BASIS 24 – Emotional Lability Subscale		X	X	X	X	
Psychiatric and Medical History/Hospital						
Treatment History Interview			X	X	X	
Alcohol and Drug Involvement						
Alcohol and Drug Use – Quantity and Frequency		X	X	X	X	

Focus Group Follow-up Sub-study. We recognize that, depending on the results of this clinical trial, we may want to contact participants after their last scheduled follow-up interview, to ask if they would be interested in participating in a small, focus group study, so that the we might learn more about their experiences with smoking and quitting following psychiatric discharge. If we go ahead with this study, we would submit a detailed IRB addendum or a separate IRB protocol, if required. However, at this point, we would add to the Consent for Participation in Research form, two checkboxes for participants to indicate either that they agree to be recontacted by the researchers for participation in this small focus group study or they do not agree to be recontacted for this purpose.

Patient Referral and Screening

All patients will be referred into the study by their attending psychiatrist at Seton Shoal Creek Hospital. Screening procedures will include a review of the medical record of all patients referred into the study, to determine if they meet eligibility criteria, including medical exclusions for the use of NRT, although most patients will already be receiving NRT during their hospital stay.

Having received the attending psychiatrist's referral and screened the medical record and determined preliminary eligibility, the study research assistant will administer the Mini Mental State Examination (MMSE; [23]) to the patient. The MMSE is a well validated and widely used screening exam for the detection of cognitive impairment ([23]). Any patient who scores less than 24 on the MMSE will be deemed ineligible to participate in the study. A score on the MMSE <24 is the generally accepted cutoff indicating the presence of cognitive impairment. A score of 24 or above is indicative of the absence cognitive impairment.

Smoking History/Motivation to Quit/Self-Efficacy, Nicotine Dependence, and Nicotine Withdrawal

Patients will provide a brief smoking history including years smoked, rate, nicotine dependence (6-item Fagerström Test for Nicotine Dependence, FTND [24]), quit attempts, and smoking cessation treatments used previously. They will also complete the 4-item Thoughts About Abstinence Scale [25], adapted from Marlatt [26], that assesses commitment, desire, and expected success/difficulty with abstinence.

Primary Outcome – Smoking Behavior

The primary measure of smoking behavior will be self-reported nonsmoking for the past 7 days (i.e., 7-day point prevalence abstinence, PPA) verified at 6- and 12-months by saliva cotinine analysis (≥15 ng/ml cutoff) [27]. We will also assess sustained tobacco abstinence and duration of continuous tobacco abstinence after hospital discharge (i.e., time to first lapse). Because NRT use produces a false positive cotinine, expired carbon monoxide (CO) (≥8 ppm cutoff) will be substituted for cotinine in those reporting NRT use during the past 7 days. As stated earlier, at the 6- and 12-month follow-ups, we will offer participants a $40 incentive for returning to Seton Shoal Creek Hospital to provide a saliva and/or breath sample. Participants who self-report smoking, do not provide a saliva or breath sample, whose cotinine or CO measures exceed the cut-offs, or who are lost to follow-up will be counted as smokers [27-29].

Because self-reported nonsmokers can fail to provide saliva or breath samples for reasons other than misrepresentation of smoking, validation of nonsmoking status by asking a significant other ("proxy validation") is an alternative validation strategy. Some trials in hospitalized smokers used it as a back-up strategy when a biochemical sample was not obtained [30-34]. As a secondary outcome measure, we will calculate self-reported point prevalence abstinence verified by either saliva cotinine or proxy validation.

Smoking Cessation Treatment Use and Adherence

At each follow-up, participants will report on their use of either counseling or pharmacotherapy or both modalities at each follow-up. Smoking cessation counseling is defined as telephone or in-person counseling from any source including a physician; pharmacotherapy includes use of NRT (nicotine patch, gum, lozenge, inhaler, or nasal spray), bupropion, or varenicline. Outcome measures include pharmacotherapy (any use, # weeks of use, use for ≥1 month) and counseling (any use, number of contacts, contact for >1 month).

Health and Health Care Utilization Outcomes

Psychiatric Symptoms**.** Depressive symptoms will be assessed using the 8 items short form (Depression 8a Participant Version) of the Patient Reported Outcomes Measurement Information System (PROMIS; [35, 36]). Anxiety symptoms will be assessed using the 8 item short form (Anxiety 8a Participant Version) of the PROMIS [35, 36]. PROMIS measures are the result of an NIH collaborative project and possess high reliability and validity [35, 36]. Psychotic symptoms will be assessed using the 4-item Psychotic subscale of the Behavior and Symptoms Identification Scale–24 (BASIS–24; [37]). Emotional lability will be assessed using the 3-item subscale of the BASIS-24 [37].

Psychiatric and Medical History / Hospital course. Primary and secondary discharge diagnoses, length of stay, type of insurance, discharge medications, and readmissions to Seton Shoal Creek Hospital will be abstracted from the patient's medical record. Participants will provide information about non-smoking related treatments e.g., medical and psychiatric inpatient hospitalizations and emergency room (ER) visits. Smoking cessation medication usage will be tracked at each follow-up interview in both study arms.

Healthcare Utilization. In order to examine potential differences in heathcare costs following intervention, we will collect data on psychiatric and medical hospital admissions and psychiatric and medical emergency room visits over the course of the 1-year following hospital discharge. We will do this by accessing available data within the Seton Healthcare Family and via self-report.

Alcohol and Drug Involvement

We will assess alcohol and drug use frequency and quantity using a series of questions that have been utilized in prior tobacco research [38].

Treatment Fidelity

The social workers/smoking counselors will follow written manuals for the SusC in-hospital sessions to ensure standard delivery of these sessions over the course of the study. All in-hospital sessions will be audiotaped and a random subset of 15% will be rated by independent raters to assess protocol adherence, with a checklist system used in prior trials [39].

Data Analysis Plan – From Grant Application - 1R01MH104562

Data Analysis Overview

As a first step, the equivalence of the random assignment of groups with regard to key baseline characteristics will be assessed. Other preliminary data analyses will include studies of patterns of missing data, research dropout rates, distributional properties of dependent and other measures, and correlations among outcome measures. Should groups differ on any characteristic, these variables will be used as covariates in the primary outcome analyses.

Primary Aims

Aim A.1.a. Tests of the effects of treatment on the primary outcome variable (7-day PPA at 6-, and 12-month post-quit) will be conducted using Generalized Estimating Equations (GEE) [40] [41]. As recommended by an SRNT working group [42], GEE is a method of repeated measures analyses for categorical outcomes that allows for inclusion of both categorical and continuous independent variables and for appropriate modeling of covariance structures when observations are correlated across time. The primary, between groups, independent variable in the GEE analysis is treatment group assignment, controlling for gender and nicotine dependence (FTND). The test of this effect is designed to answer the question, "When compared to BE, does ExC result in superior, long-term cessation outcomes in SMI smokers?"

Analyses will be conducted following the intention-to-treat principle. All subjects who have been randomized to treatment will be included in the analyses, with those lost to follow-up counted as smoking. This is the most conservative approach and represents our main outcome analysis.

Aim A.1.b. Multinomial logistic regression will be used to determine whether the proportion of patients that used evidence-based smoking cessation treatment (counseling and/or medication) in the month after discharge is higher in Extended Care vs. Brief Education (Aim A.1.b.). In a multinomial logistic regression model, the patients who did not use any treatment will be set as the reference group such that differences in the proportion of patients who used any treatment (counseling or medication vs. no treatment) and combined treatments (counseling and medication vs. no treatment) between interventions (ExC vs. BE) will be tested. Differences in participants' self-reported frequency of treatment use will also be examined using separate linear regression models. We will report odds ratios and Cohen's d [144] as the effect sizes.

6. Participants

a. Target Population

Participants (n = 422) will be recruited from among adult psychiatric inpatients at Seton Shoal Creek Hospital in Austin, Texas. Individuals with psychiatric disorders have disproportionately high rates of cigarette smoking and society will benefit from the development of new interventions to assist these individuals to quit smoking.

b. Inclusion/Exclusion

Participants (n = 422) will be recruited from the adult psychiatric inpatient units at Seton Shoal Creek Hospital in Austin, Texas. Inclusion criteria: (a) >18 years of age, and (b) current smoker (i.e., at least 5 cigarettes/day when not hospitalized). Exclusion criteria: (a) current diagnosis of dementia or other cognitive impairment that would limit study participation, (b) Mini-Mental State Examination (MMSE: [23]) score < 24, (c) patient's inability to provide consent for study participation due to his/her inability to demonstrate an understanding of study procedures as contained in the statement of informed consent, after no more than two explanations, (d) current diagnosis of mental retardation or autistic disorder, (e) current diagnosis of a (non-nicotine) substance use disorder requiring detoxification, (f) no access to a telephone or inability to communicate by telephone, (g) planned discharge to institutional care (e.g., nursing home, long-term rehab, jail, etc., (h) no current or stable mailing address, (i) medical contraindication for the use of nicotine replacement therapy (NRT) and (j) pregnancy, breastfeeding, or plans to become pregnant within 6 months. All exclusions for psychiatric diagnosis above will be based upon the clinical diagnosis as recorded in the Seton Shoal Creek Hospital medical record.

c. Benefits

The anticipated benefits of the study are twofold: 1) There is the potential for participants to receive benefit from their study participation. All participants in both conditions (Sustained Care and Usual Care) will be assessed on various factors related to their cigarette smoking and will be followed over a 12 month period to assess possible changes in their smoking status, thereby potentially increasing their knowledge of their cigarette smoking and related issues. Participants in both conditions will receive information about and be encouraged to use evidence-based smoking cessation treatment. Thus by participating in this project, there is the potential that participants may benefit in terms of increased knowledge about their smoking and/or in terms of helping them to quit smoking; 2) the results of the study will be used to advance understanding of factors related to smoking cessation among smokers in inpatient psychiatric treatment and will have considerable potential public health significance by determining whether the proposed Sustained Care intervention effectively motivates sustained abstinence after hospital discharge.

d. Risks

Potential risks include:

1. Risk of side effects from use of Nicotine Patch
2. Risk of Nicotine Withdrawal
3. Risk of suicidality/homicidality identified at follow-up time points
4. Risk of breach of confidentiality and loss of privacy
5. Risk that participants may feel coerced to participate in the study

Risk of Side Effects from use of Nicotine Patch

Risks. More common side effects of nicotine patch use include local skin irritation at the site of the patch, nausea, and disturbed and vivid dreams. Less common are allergic skin reactions.

Minimization. In order to protect against risk from pharmacotherapy usage, this study will only use nicotine patches, which are FDA-approved, and readily available as over-the-counter smoking cessation medications. Written and verbal instructions will be provided to patients given prescriptions for medication to contact the research study staff or their primary physician in case of adverse side effects from NRT use. Patients' outpatient psychiatrist and primary care physician will be sent a letter to inform them of patients' study participation and use of the nicotine patch. At the 1-month follow-up assessment call, the research assistant will screen for adverse events. Ultimately, the PIs will review any serious adverse events and report them appropriately to the University of Texas at Austin and Seton Healthcare Family IRBs and to NIMH.

Risk of Nicotine Withdrawal

Risks. For those participants attempting to quit smoking, there is a strong likelihood that they will experience some nicotine withdrawal symptoms, including anxiety, restlessness, anger, irritability, sadness, problems concentrating, appetite change and weight gain, insomnia, and decreased heart rate.

Minimization. If making a quit attempt, participants will be encouraged to also use nicotine replacement therapy which should diminish the overall severity of withdrawal discomfort, although not necessarily eliminate withdrawal discomfort entirely. Moreover, withdrawal symptoms are usually short-lived, with most symptoms abating within 1-2 weeks.

Risk of suicidality/homicidality identified at follow-up time points

Risks. Although unlikely to be caused by study participation, in this type of patient population, the risk of suicide or homicide is always present.

Minimization. Inpatient psychiatric units at Seton Shoal Creek Hospital are well equipped to manage patients at risk of suicide. All staff are fully trained to ascertain safety of patients and reduce their suicide risk. Moreover, all research staff that have direct involvement with patients will be fully trained by Seton Shoal Creek Hospital in procedures for assessment and intervention in cases where suicidal or homicidal ideation is expressed. If such cases occur during the course of the patient's hospitalization, research staff will immediately contact the clinical staff in the inpatient units. Appropriate clinical action will be taken in such circumstances, as determined by the patient's attending physician and the treatment team. If such cases occur during follow-up contacts (i.e., after inpatient hospitalization), research staff will immediately contact a Seton Shoal Creek psychiatrist, who will be on-call at all times, who will take appropriate clinical action.

Risk of breach of confidentiality and loss of privacy

Risks. The risk of loss of privacy is judged to be minimal.

Minimization. The informed consent document will state clearly to patients that the study is being done as a collaboration between the University of Texas at Austin and Seton Healthcare Family, TelASK, a company that makes automated phone calls; and Alere Wellbeing, a company that provides smoking cessation quitline counseling, along with web-based and text-based quit coaching resources. Participants will be informed that in order to make the phone calls, TelASK will be given their name, phone number, address, smoking status, and the date that they are discharged from the hospital but not any other protected information. Alere Wellbeing will be given their name, phone number, address, discharge date and information collected about their smoking behavior that has been collected as part of the research study. This is done to aid the Alere Wellbeing smoking counselors to provide counseling that is targeted to their smoking cessation needs.

Patients will be informed that information exchanged between the University of Texas at Austin, Seton Healthcare Family and the outside entities will be sent by way of a secure password-protected server. Data collected directly from participants and data abstracted from participants' medical records will be entered and tracked at Seton Shoal Creek Hospital using a University of Texas at Austin REDCap (Research Electronic Data Capture) account. REDCap is a secure, web application designed to support data capture securely for research studies, including Category I data (per the UT REDCap webpage), providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap also provides a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. The system was developed by a multi-institutional consortium that includes University of Texas at Austin and was initiated at Vanderbilt University. The database is hosted at the Population Research Center, which will be used as a central location for data processing and management. The PRC server has been cleared for Category-I data collection by UT's Information Security Office. Network transmissions (data entry, survey submission, web browsing, etc.) in REDCap are protected via Secure Sockets Layer (SSL) encryption. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the PRC. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap provides a secure, web-based application that is flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules at the time of entry.

Also, names will not be included on audio recordings or in any published reports. Electronic data, including audio files, will be stored on a secure, multi-layered password-protected server, UT Box, which is also authorized to safely store Category I data. Consent forms and any paper data will be stored in a locked file cabinet within a locked office. All staff are or will be fully trained by the Principal Investigator in relevant ethical principles and procedures, particularly around confidentiality. All audio recordings will be erased upon completion of data analysis.

We ensure local confidentiality by requiring rotating password access to client machines. Lastly, only the PI and the project director will have access privileges to export requested data. During the study, TelASK and Alere Wellbeing will establish a secure website to view call results in real time, quit statuses and counseling requests. Data will be transferred through a secure FTP (both to TelASK and Alere Wellbeing). Neither TelASK or Alere Wellbeing will share any patient information with any outside organizations or entities. Within one year of the completion of the study, all patient data will be purged from TelASK's data files. Alere Wellbeing will maintain any business records, per their standard procedures, that may include data provided by the investigators (for example, records of participants who receive clinical services from Alere Wellbeing). This will allow them to provide optimal service to these individuals, should they later call the State of Texas Tobacco Quitline, whose services are provided by Alere Wellbeing. Alere Wellbeing is a HIPAA-covered entity and has procedures in place to maintain the security of all study data, including PHI.

Risk that participants may feel coerced to participate in the study

Risks. Issues related to coercion are unlikely since any patient's decision not to participate in the study will not influence their current treatment in the Seton Shoal Creek Hospital inpatient psychiatric units nor will it influence their future treatment or standing with the Seton Healthcare Family.

Minimization. In order to minimize the risk of potential coercion, written informed consent must be obtained from each participant prior to entering the study. The informed consent document will explain, in simple terms, before the participant is entered into the study, the risks and benefits to the participant. The informed consent document will contain a statement that the consent is freely given, that the participant is aware of the risks and benefits of entering the study, and that the participant is free to withdraw from the study at any time. Patients will be told and it is stated in the consent form that patients may refuse to answer any survey or interview questions. All patients will be instructed that their decision as to whether to participate in the study will not influence their current or future standing with Seton Shoal Creek Hospital or their treatment in the psychiatric inpatient units. Consent will be obtained after a thorough explanation of the study by research staff and opportunity for the participant to ask questions about the study. The IRB-approved consent document will be signed and dated by the participant and research staff member. The signed informed consent document will be retained with study records. Each participant will be given a copy of his or her signed informed consent.

e. Recruitment

f. All patients will be referred into the study by their attending psychiatrist at Seton Shoal Creek Hospital. Screening procedures will include a review of the medical record of all patients referred into the study, to determine if they meet eligibility criteria. The research coordinator will then approach the patient to explain the study procedures and determine if they are interesting in participating in the study.

As "discussed by email" and confirmed in an email to me from Sandra Borucki on 4/23/15, the patient record review and recruitment process has be modified to describe the acceptable procedure (attending physician referral, medical record review, approach potential subject for recruitment purposes). Being able to review the patient medical records after the MD referral but prior to approaching them, will assure that we will be able to rule patients out for certain diagnoses, and thus not have to do so after they are already recruited into the study. All procedures in the IRB protocol have been modified accordingly.

g. Obtaining Informed Consent

a) IRB Authorized Waiver of HIPAA Authorization and consent for medical record review: the purpose is to determine eligibility status, especially with regard to the following:

(1) current diagnosis of mental retardation or autistic disorder, (2) current primary diagnosis of a (non-nicotine) substance use disorder, and (3) planned discharge to institutional care (e.g., nursing home, long-term rehab, etc.).

The justification is as follows:

· The first two are needed, as patients do not always know their diagnoses. The third is important, as patients may not always be fully aware of plans to discharge them to institutional care.

· Clearly, it would be a disservice to patients to consent them into the study, only to then review the medical record and find out that they need to be excluded.

b) HIPAA Authorization for Research: the document will be signed by the subject to grant access to the complete existing health record until 12 months after the completion of the study.

c) In a study such as this, it is critical to be certain that participants are cognitively able to consent to study participation during their acute psychiatric hospitalization. We will utilize a three-faceted approach to assure that patients are cognitively able to provide consent during their acute hospitalization:

1. Prior to approaching any patient about possible study participation, we will consult with nursing staff

on the inpatient unit to obtain their opinion of whether the patient is cognitively able to provide informed consent and participate in the study. We will also require approval by the attending psychiatrist prior to approaching a patient for possible study recruitment.

2. Having received the attending psychiatrist's permission to approach the patient, the study research coordinator will administer the Mini Mental State Examination (MMSE; [23]) to the patient. Any patient who scores less than 24 on the MMSE will be deemed ineligible to participate in the study. A score of 24 or above is indicative of the absence of cognitive impairment.

3. We will utilize a process called *iterative feedback* [43] in order to ensure that patients fully understand the various aspects of their involvement in the study. A research coordinator, trained by the Principal Investigator, will provide the patient with a copy of the consent form and will provide a careful explanation of all aspects and details covered in the written consent. The research coordinator will then assess whether or not the patient understands the consent form and study procedures by querying the patient via open-ended questions about important aspects of the study protocol to assess his/her understanding of the procedures. "Understanding the consent and study procedures" will be defined by the ability of the patient to accurately answer this series of questions about the study procedure, based upon what was explained to them.

If the patient answers any questions incorrectly, the interviewer will review the relevant section(s) of the consent form a second time and query the patient again to determine whether he/she can provide an accurate response reflecting an understanding of that aspect of the study. If the patient still cannot demonstrate an understanding of the study procedure upon which he/she is queried after a second explanation, the patient will be deemed ineligible to participate in the study.

4. Therefore, in order to be eligible for study participation, patients must: a) not have an MMSE score < 24, and b) must be able to demonstrate an understanding of study procedures contained in the statement of informed consent after no more than two explanations.

7. Privacy and Confidentiality

As described above (in Risks "6.d.4." - Risk of breach of confidentiality and loss of privacy), data collected directly from participants and data abstracted from participants' medical records will be entered and tracked at Seton Shoal Creek Hospital using a University of Texas at Austin REDCap (Research Electronic Data Capture) account. REDCap is a secure, web application designed to support data capture securely for research studies, including Category I data (per the UT REDCap webpage), providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Data collected from participants and exchanged between the University of Texas at Austin, Seton Healthcare Family and the outside entities will be sent by way of a secure password-protected server (UT Box). All participant identifiable information will be destroyed within 12 months from the completion of the study.

Also, names will not be included on audio recordings or in any published reports. Electronic data, including audio files, will be stored on a secure, multi-layered password-protected server, UT Box, which is also authorized to safely store Category I data. Consent forms and any paper data will be

stored in a locked file cabinet within a locked office. All staff are or will be fully trained by the Principal Investigator in relevant ethical principles and procedures, particularly around confidentiality. All audio recordings will be destroyed 6 months after the end of the study.

Neither TelASK nor Alere Wellbeing will share any patient information with any outside organizations or entities. Within one year of the completion of the study, all patient data will be purged from TelASK's data files. Alere Wellbeing will maintain any business records, per their standard procedures, that may include data provided by the investigators (for example, records of participants who receive clinical services from Alere Wellbeing). This will allow them to provide optimal service to these individuals, should they later call the State of Texas Tobacco Quitline, whose services are provided by Alere Wellbeing. Alere Wellbeing is a HIPAA-covered entity and has procedures in place to maintain the security of all study data, including PHI.

Saliva samples will be collected and frozen in a locked freezer at Seton Healthcare Family, in preparation for sending, in batches, to a laboratory (Salimetrics, State College, PA) for analysis of cotinine levels. The saliva samples will be identified to the laboratory by only a numerical identifier and the samples will be destroyed at the laboratory according to their standard laboratory protocol following sample analysis. No saliva samples will be maintained at Seton beyond 12 months after the completion of the last 12-month follow-up.

8. Compensation

Participants will be compensated for completing follow-up interviews using ClinCards, a MasterCard product that allows researchers to upload participant payments via a web portal. Participant payments will be in the following amounts: $5 upon hospital discharge for completion of the baseline assessment, $30 at the 1- and 3-month follow-ups and $60 at the 6-month follow-up. We will also conduct a 12-month follow-up for those participants who report 7-day point prevalence abstinence, confirmed biochemically, at the 6-month follow-up. Participants for whom a 12-month follow-up is requested, will be compensated $60 for completion of this follow-up. In addition, those participants who report 7-day point prevalence smoking abstinence at the 6-month follow-up (or 12-month follow-up, if applicable) will be asked to return to Seton Shoal Creek Hospital to provide carbon monoxide and saliva samples for biochemical verification of abstinence, and will be compensated $40 (via ClinCards) for doing so. We expect that on the order of 15% of participants or less will report smoking abstinence and the payment is intended to compensate them for their additional time, effort and expense of returning to the hospital.

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