Mobile Health Technology to Enhance Abstinence in Smokers With Schizophrenia

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SPECIFIC AIMS

Cigarette smoking is the most lethal substance use disorder in the United States in terms of morbidity and mortality, and accounts for 1 of every 5 deaths each year (Centers for Disease Control and Prevention, 2008; Mokdad, Marks, Stroup, & Gerberding, 2004). Individuals diagnosed with schizophrenia smoke at a fourfold rate (80% versus 20%) compared to the general population (de Leon & Diaz, 2005; Keltner & Grant, 2006). Unfortunately, efforts to successfully decrease smoking among individuals with schizophrenia have been limited. There is a clear need to develop innovative approaches that increase the efficacy of smoking cessation interventions for patients with schizophrenia. Our long term goal is to implement innovative and effective interventions that increase access and utilization of evidence-based smoking cessation treatment for patients with mental illness.

The addition of mobile health (mHealth) technology could provide a low cost method to increase the feasibility and reach of evidence-based smoking cessation principles and treatment. Multi-Component Mobile-enhanced Treatment for Smoking Cessation (iCOMMIT) is a smoking cessation treatment that combines mobile technology with behavioral, cognitive-behavioral, and pharmacologic approaches shown to improve smoking cessation outcomes. The components of the intervention include 1) behavioral therapy in the form of mobile contingency management (mCM) designed to increase early abstinent rates; 2) pharmacotherapy for smoking cessation [including nicotine replacement therapy (NRT) and bupropion or varenicline]; 3) five to nine sessions of guideline based cognitive-behavioral smoking cessation counseling designed to increased coping skills specific to smoking cessation; and 4) SMS text messaging reminders to increase medication adherence. The *overall objective* of the current study is to refine the components of iCOMMIT and evaluate the feasibility of the treatment approach in smokers with schizophrenia. Specific aims are to:

AIM 1. ***Refine a multi-component smoking cessation intervention, entitled iCOMMIT, for smokers with schizophrenia****.* A successive cohort design will be used to refine the existing therapist manual, participant workbook, text messages, and the mCM mobile phone app for smokers diagnosed with schizophrenia, schizoaffective disorder or psychotic disorder. Two cohorts of smokers will complete the intervention. Quantitative and qualitative data from therapists and participants will be utilized to modify the treatment components including the therapist manual, participant workbook, and mobile applications and procedures after each cohort.

AIM 2. ***Evaluate the feasibility and acceptability of iCOMMIT among smokers with schizophrenia.*** Measures of intervention feasibility, treatment acceptability, and participant content knowledge upon treatment completion will be used to describe the feasibility and acceptability of iCOMMIT.

AIM 3. ***Evaluate the feasibility of recruitment, randomization and retention procedures in a pilot randomized clinical trial comparing iCOMMIT to a standard treatment control for improving smoking cessation outcomes.*** The feasibility of recruitment, randomization, and retention will be assessed in a pilot RCT comparing iCOMMIT to standard treatment [bupropion and NRT (or varenicline for treatment non-responders), and five to nine counseling sessions). The primary clinical end-point will be self-reported and bio-verified prolonged abstinence at a 6-month follow-up. Measures of recruitment (proportion screened versus enrolled), randomization (drop-outs immediately upon randomization), and retention (proportion of treatment completers) will assess feasibility of the study procedures. Thirty-six smokers with schizophrenia will be randomized in a 2:1 ratio to iCOMMIT versus a standard care condition.

AIM 4: ***Evaluate potential treatment mediators and moderators*****.** We will begin to explore putative iCOMMIT treatment mediators (self-efficacy, delay discounting, treatment process mechanisms [treatment completion, medication adherence], positive and negative symptoms of schizophrenia, depressive symptoms, and neurocognitive status) and moderators (nicotine dependence, age, race, and gender).

With regard to expected outcomes, the work proposed in these aims will provide the first step toward implementation of an innovative approach that builds upon the power of mHealth technology to reduce the prevalence of smoking in patients with schizophrenia. Our pilot data strongly suggest that it is possible to use mHealth platforms to increase the feasibility and reach of behavioral treatment (mCM) with smokers with mental illness, including those with schizophrenia. It is expected that the refinement of the iCOMMIT approach, which combines behavioral treatment with pharmacotherapy, cognitive-behavioral counseling, pharmacotherapy, and relapse prevention strategies, will result in an acceptable and feasible treatment that will optimize smoking cessation outcomes in this important population. Results

of this study will pave the way for a larger evaluation of the efficacy and cost effectiveness of the proposed treatment approach. The *positive impact* of reducing smoking among smokers with schizophrenia and other psychiatric disorders is enormous, as it will prevent significant morbidity and mortality.

A. RESEARCH STRATEGY: SIGNIFICANCE

Deaths from tobacco use are higher than the combined deaths due to AIDS, alcohol, motor vehicles, homicide, drugs, and suicide (Centers for Disease Control and Prevention, 2004). Despite representing 22% of the adult U.S. population, individuals with psychiatric conditions consume almost half of all cigarettes sold in the United States, and persons with schizophrenia are at particular risk due to increased rates of tobacco use and greater difficulty stopping smoking and maintaining abstinence (Lasser et al., 2000). Although it is estimated that 80% of individuals with schizophrenia smoke cigarettes, nearly 40% (38.9%) report having tried to quit in the preceding year (McClave, McKnight-Eily, Davis, & Dube, 2010). It has been suggested that smokers with schizophrenia need more intensive treatment options than current approaches (Selby, Voci, Zawertailo, George, & Brands, 2010).

There is a need to develop smoking cessation models that will improve both short and long term quit rates among smokers with schizophrenia, provide more practical interventions that reduce clinical and therapist time, and increase the reach of existing evidence-based practices. The current application builds upon advances in mHealth technology to refine procedures for a multi-component treatment for smoking cessation we call iCOMMIT. We expect that mCM (using an application we developed for the smart phone) paired with smoking cessation pharmacotherapy and counseling, will significantly improve both short and long term quit rates among smokers with schizophrenia.

B. RESEARCH STRATEGY: INNOVATION

The proposed research is innovative because it will be the first study to combine mHealth applications with evidence-based smoking cessation treatment with the aim of increasing both short-term and long-term quit rates in smokers with schizophrenia. Our preliminary study (see Preliminary Data subsection) strongly suggests that mCM improves abstinence rates among another psychiatric smoker group, i.e., those with PTSD (Hertzberg et al., 2014). We expect that mCM keeps participants engaged in treatment, resulting in completion of more counseling sessions and greater likelihood of optimal medication adherence, both of which have been predictive of long term abstinence (Bastian et al., 2012; Alterman, Gariti, Cook, & Cnaan, 1999; Balmford, Borland, Hammond, & Cummings, 2011; Cooper et al., 2004). Given that the current proposed project also involves using a successive cohort design to specifically tailor the intervention to smokers with schizophrenia, results could provide a model for modifying treatments for this difficult to treat population. The innovative aspects of the research (i.e., successive cohort design, mCM, and its combination with evidence-based health change interventions) stand to make considerable contributions to research in other hard to treat populations (e.g., other psychiatric disorders, low income smokers).

C. RESEARCH STRATEGY: APPROACH

C.1. Schizophrenia and Smoking

Although prevalence rates of smoking for individuals with schizophrenia vary by study setting and psychiatric comorbidity, about 70%-85% of individuals with schizophrenia use tobacco (Ziedonis et al., 2008). Correspondingly, individuals with schizophrenia have increased mortality rates compared to the general population and this alarming gap has gotten worse in the past three decades (Saha, Chant, & McGrath, 2007). Approximately half of the 25 years of shortened life span associated with schizophrenia is attributable to smoking (George & Ziedonis, 2009).

C.2. Current Treatment Approaches to Smoking for Persons with Schizophrenia

The U.S. Department of Health and Human Services' clinical practice guidelines stress the importance of treating individuals with mental illness for smoking cessation and recommend that persons with mental illness receive the same treatments as the general population (Fiore et al., 2008). A recent Cochrane review (Tsoi, Porwal, & Webster, 2013) has examined the efficacy of smoking cessation strategies in smokers with schizophrenia. Several trials have now demonstrated the efficacy and safety of bupropion SR. A meta-analysis of seven placebo controlled trials of bupropion SR suggests that bupropion is significantly associated with increased cessation rates at the end of treatment and at long term (6 month) follow-ups compared to placebo (RR 2.78: 95% CI 1.02-7.58; Tsoi, Porwal, & Webster, 2010). Bupropion SR was not found to lead to significant differences in positive, negative or depressive symptoms compared to placebo (Tsoi, Porwal, & Webster, 2010). Several recent studies have suggested that varenicline is associated with increased

cessation rates (Weiner et al., 2011; Stapleton et al., 2008; Williams et al., 2012). In a recent meta-analysis of 16 publications describing varenicline use among smokers with schizophrenia, varenicline was not associated with worsening of psychiatric symptoms in closely monitored patients (Cerimele & Durango, 2012). Other studies suggest that varenicline use among smokers with schizophrenia is not associated with an increase in adverse events when compared with NRT and counseling (Stapleton et al., 2008) or with placebo (Williams, et al., 2012). There is evidence, also, that NRT in combination with behavioral treatment comprised of contingent reinforcement is associated with increased abstinence (Gallagher, Penn, Schindler, & Layne, 2007). Similarly, NRT in combination with atypical antipsychotic medication can increase abstinence rates compared with standard antipsychotics (George et al., 2000).

C.3. Contingency Management and Delay Discounting among Persons with Schizophrenia

Contingency management can be conceptualized within a behavioral neuroeconomic framework (Glimcher & Rustichini, 2004; Potenza, Sofuoglu, Carroll, & Rounsaville, 2011). Individuals with addictions typically place greater value on immediate awards (e.g., psychological and physiological effects of a drug) and rapidly devalue future rewards (e.g., improved health outcomes). This process is termed temporal or *delay discounting,* and has been observed across a variety of addictions and various types of reinforcement (e.g., drugs, money). Steep delay discounting has been associated with poor addiction treatment outcomes (Krishnan-Sarin et al., 2006). There is also evidence among smokers that delay discounting can be diminished by establishing abstinence from smoking (Petry, 2001).

Our approach was also informed by neurobiological research that provides a theoretical foundation as to why combining an established CM paradigm with mobile health applications may be a particularly powerful approach to smoking cessation for individuals with schizophrenia (Potenza et al., 2011; Elman et al., 2005; Hopper et al., 2008). Briefly, a dopaminergic reward processing network including the ventral tegmental area (VTA), striatum, nucleus accumbens, hippocampus, dorsolateral prefrontal cortex, and ventromedial prefrontal cortex has been established as fundamental to the processing of both drug and non-drug related rewards (Schultz, 2006). Recent research has suggested that persons with schizophrenia demonstrate an imbalance within this dopamine reward system including decreased dopamine in the prefrontal cortex, deficient regulation of dopamine in the nucleus accumbens by the hippocampus, and increased dopamine in the striatum. This imbalance contributes to positive and negative symptoms of schizophrenia (Howes & Kapur, 2009), and to a parallel vulnerability to substance abuse (Chambers, Krystal, & Self, 2001). At the cortical level, deficits in prefrontal dopamine contribute to the executive functioning problems often observed in schizophrenia, as well as to diminished inhibitory control over compulsive drug-related behaviors (Sailer et al., 2008). At the subcortical level, excessive dopamine increases the "noise" in the reward processing system in individuals with schizophrenia, such that dopamine signaling the presence of potentially rewarding environmental stimuli may be "drowned out" (Howes & Kapur, 2009). This lack of sensitivity contributes to the development of negative symptoms of schizophrenia, as well as to diminished sensitivity to feedback and to naturally occurring (i.e. non-drug related) rewarding stimuli (Howes & Kapur, 2009; Rausch et al., 2014). *As such, in order to reduce smoking among persons with schizophrenia, there is a need to provide immediate positive highly salient alternative reinforcers to substance use, as well as cognitive-behavior therapy to strengthen their ability to inhibit compulsive use*. The proposed use of mobile CM accomplishes just that.

mCM will provide immediate feedback and a sufficiently salient reward (money) to overcome the "noise" within the system, and to activate dopamine-mediated reinforcement at the subcortical level. Simultaneously, mCM is expected to address frontally-mediated inhibitory control deficits through building skills that will increase in self-efficacy and counteract problems with delay discounting observed with periods of early abstinence. *In the current project, we will explore the effect of early abstinence on delay discounting and self-efficacy.* With sustained abstinence, the hedonic association between smoking behavior and dopamine-mediated reward is extinguished, while the association between non-drug seeking/using behaviors and alternative rewards learned through CBT (e.g., engaging in other pleasurable activities) is strengthened.

C.4. Limitations of Contingency Management for Smoking Cessation

Previous trials examining behavioral treatments comprised of CM approaches for smokers with schizophrenia show promise for short term outcomes (Tidey, Rohsenow, Kaplan, Swift, & Reid, 2011; Tsoi, Porwal & Webster, 2010; Gallagher et al., 2007). Several studies examining CM interventions have found no difference between intervention and controls when examining long-term abstinence rates once the contingencies have been removed (Petry, 2010). While

most CM studies have not been adequately powered to detect differences in long-term quit-rates (Petry, 2010), available evidence would suggest that most CM interventions are not likely to be effective for long term abstinence if used in isolation.

C.5. Overcoming the Limitations: The Need for Multi-Component Smoking Cessation Interventions

While CM alone may not have significant effects on long term abstinence rates, there is little debate that CM helps retain difficult-to-treat populations and lead them to achieve initial abstinence. Further, there is evidence that CM and associated reductions in smoking lead to increased feelings of self-efficacy (Romanowich, Mintz & Lamb, 2009), which if paired with other relapse prevention supports, may help individuals sustain a successful quit attempt. In this context, an ideal strategy would be to integrate CM with other evidence- based forms of smoking cessation treatment. There is a surprising lack of research aimed at evaluating multi-component smoking cessation interventions that integrate CM with evidence-based cognitive-behavioral treatment (CBT) and smoking cessation aids (e.g., NRT or other medications). We expect that mCM will result in increased early abstinence and, in combination with evidence-based cognitive-behavioral and pharmacologic smoking cessation treatment, SMS text reminders to increase medication adherence, and an mHealth relapse prevention application, will result in increased long term abstinence rates among smokers with schizophrenia. The current proposed project will allow us to effectively revise the treatment procedures and manuals to maximize efficacy with this patient group.

C.6. Preliminary Data

Our laboratory has extensive experience with the proposed methods of identifying, contacting, and conducting clinical trials with psychiatric smokers. We have recently expanded our smoking cessation work to homeless smokers and have collected pilot data with a sample of 20 homeless smokers that included 4 smokers with schizophrenia (Carpenter et al., 2014). While the small sample of smokers with schizophrenia is too small to provide any reliable information about effect sizes, we have collected valuable data that informs this application. Important information we learned from the pilot work is 1) our cost estimates associated with replacing lost or damaged equipment are realistic (across 22 patients with PTSD, 20 homeless veterans and 4 homeless smokers with schizophrenia only one phone and carbon monoxide (CO) monitor was lost or damaged; an additional phone was returned for a replacement battery); 2) individuals with schizophrenia were as likely as other participants to keep up with their phones and CO monitors, and; 3) individuals with schizophrenia were fully capable of using the smart phone based application to upload videos and receive compensation (to date adherence with uploading videos for smokers with schizophrenia has been excellent; 88%). In addition, while preliminary, our initial findings suggest that mCM is a promising approach to use with this population, as we found that 50% of smokers with schizophrenia (n = 4) who received mCM were abstinent at the 6-month follow-up.

C.7. Overview and Study Design

The proposed project comprises two stages as summarized in Table 1 below. In Stage 1 (months 1-18), we will employ a successive cohort design to review and revise our current treatment manuals (therapist manual and patient workbook), as well as the other treatment components of iCOMMIT with two successive cohorts of smokers with schizophrenia. The data from these cohorts will be used to refine the manuals and procedures associated with the intervention. The refinement of the manuals and intervention procedures (e.g., changes to the mCM app) will be based on consultation among the intervention refinement team and the computer scientist who developed the mCM application.

Stage 2 (months 16-36) will consist of a pilot randomized controlled trial of the revised iCOMMIT compared to a control intervention that provides the same CBT and pharmacotherapy as iCOMMIT but does not include the mHealth applications or mCM.

Table 1. Timeline for Intervention Refinement and Testing

		Year 1				Year 2				Year 3			
Stage	**Activity**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
1	**Recruit and complete (including follow-up visits) a cohort of 5 smokers with schizophrenia to provide feedback on participant manual and intervention**												
	Revision 1: Revise manual and intervention based on participant and clinician feedback												
	Recruit and complete (including follow-up visits) an additional cohort of 10 smokers with schizophrenia to provide feedback on participant manual and intervention												
	Revision 2: Revise manual and intervention based on participant and counselor feedback and finalize manual and intervention procedures												
2	**Recruitment and screening for Stage 2 RCT participants**												
	Conduct randomized controlled trial and complete follow-up visits												
	Data analysis												

C.8. Overview of the Successive Cohort Design (SCD) Model

The successive cohort design (SCD; Epstein et al., 2012) is an iterative process designed to systematically refine and modify behavioral treatments in the early stage of development. The SCD model is appropriate for Stage 1 research, defined in NIDA's program announcement in the mid-90s that introduced 3 stages in the development of behavioral treatments (Epstein, McCrady, Morgan, Cook, Kugler, & Ziedonis, 2007; Rounsaville, Carroll, & Onken, 2001; National Institute on Drug Abuse, 2003). Stage 1 research is designed to generate or modify existing protocols and conduct preliminary testing before larger efficacy trials (Stage 2) and effectiveness research (Stage 3). The SCD involves several steps including 1) identification of a promising treatment based on current theoretical models; 2) identification of relevant treatment elements; 3) development of initial treatment manuals, supporting materials, measures and procedures; and 4) iterative revisions based on qualitative and quantitative data collected through providing the treatment to successive cohorts of patients (Epstein et al., 2007). We have already identified the treatment elements, developed mobile phone applications and supporting materials (e.g., treatment manual, participant workbook), have published initial reports of the feasibility of using mCM in patients with PTSD (Hertzberg et al., 2013) and submitted a manuscript utilizing the same approach with smokers who were homeless. We now propose to refine the treatment approach with two successive cohorts of smokers with schizophrenia, schizoaffective disorder or other psychotic disorders, and then conduct a pilot trial to test feasibility and acceptability.

C.8.1. Stage 1: Feasibility and Treatment Refinement

The first cohort of five participants will complete the iCOMMIT treatment and provide evaluative feedback during an in-depth interview administered at the end of the study. Content analysis of the resulting data will proceed as described by Zhang and Wildermuth (2009a, 2009b). A coding scheme will be developed for categorizing comments made during the interview based on the study components (i.e., mCM, CBT, NRT utility and adherence) and subcomponents (e.g., mCM feasibility, CBT burden) that they address and the evaluations drawn (e.g., CBT session too long, video upload still unclear after mCM training). Multiple coders will be trained to apply the coding scheme to example interview responses. Upon reaching satisfactory inter-rater reliability (Cohen's kappa ≥ .70), coding of the interview data will be completed. A summary of the findings will be evaluated by the treatment refinement team. Revisions will be made based on the evaluations, and then another cohort of ten patients will be treated. Qualitative

and quantitative evaluation will be completed once more as described above, and revisions will be made. The resulting iteration of the treatment will be utilized in the subsequent pilot randomized controlled trial (RCT).

C.8.2. Successive Cohort Design Stage 2: Overview of the Pilot Randomized Control Trial

After treatment modifications from cohort 2, we will conduct a pilot trial. The proposed RCT is a 2-arm trial comparing iCOMMIT to a standard control condition that will combine equivalent guideline based smoking cessation counseling, NRT and bupropion or pharmaceutical monotherapy with varenicline, but no mCM in 36 smokers with schizophrenia. The primary clinical endpoint of the RCT will be prolonged abstinence at 6 months. Study procedures and timeline are summarized in Figure 1. In addition to those procedures outlined therein, participants will be asked to attend two follow-up visits at 3 months and 6 months post-quit.

C.9. iCOMMIT Treatment Components, Procedures and Rationale

***C.9.1. mCM Procedures*.** iCOMMIT participants will receive monetary compensation based on their own reduced CO readings. iCOMMIT participants will receive training in use of the smart phone and CO monitor. Participants will be instructed to provide video recordings of CO readings using an Apple iPhone smart phone or a Droid MAXX 2. The iPhone is equipped with an 8 megapixel video camera with DVD quality video (1920 x 1080 resolution), with 30 frames-per-second capture. The MAXX 2 has an octa-core 1.7 Ghz processor, 2 GB RAM, and 5.5" full HD display. The operating system (OS) being utilized for the smart phones is Android 5.1.1 Lollipop, see FIPS 140-2 certificate 1998. The CO breath monitor, the iCO Smokerlyzer, is abattery operated instrument that measures CO in ppm (http://www.bedfont.com/shop/smokerlyzer/ico_smokerlyzer). The Bedfont/coVita iCO™ Smokerlyzer® plugs into a smart phone by means of the headphone jack, and communicates with the smart phone app developed by our team. Participants are able to see the CO reading within the app, and the app collects the CO data directly. Data are stored in the same manner as the videorecordings that participants upload (see below and in "Protection From Risks: Data Security" herein).

With regards to FDA device issues, Bedfont/coVita will not be seeking 510k Clearance on the iCO™ Smokerlyzer® because it does not meet the standard/criteria of a medical device. Device manufacturers are required to follow FDA guidance to inform them of when a device necessitates 510k application. Per Jason Aversano at Bedfont/coVita, their regulatory team has determined that this is not necessary primarily because they do not make a medical claim about the device, as it is not designed to diagnose a disease or illness. Simply measuring CO is not diagnosing a disease or illness and we make no medical claim on the iCO™ Smokerlyer® that it can be used to screen for CO poisoning.

For each video recording, participants will be asked to 1) use a nose clip to prevent cheating by inhaling fresh air slowly through the nose while puffing; 2) begin a recording using the phone; 3) show the initial zero CO reading to the camera; 4) video record him/herself holding his/her breath during the monitor's countdown; 5) audibly blow slowly into the CO monitor while on camera; and 6) show the final CO reading to the camera. This procedure has worked well in our pilot studies. Please note that although the CO data are collected by the smart phone app, videorecording is still crucial to the study's procedures because verification that the study participant is the person providing the CO reading is of utmost importance. Please see "Protection From Risks: Data Security" for a full description of the information security profiles of the devices used, transmission of data, and storage thereof.

Participants will practice this data collection in the baseline session and for one week prior to their quit date to ensure they can effectively complete mCM procedures. They will be instructed to take two readings per 24-hour period, with at least eight hours between each sample. Video recordings are uploaded to a secure server *via* the smart phone based app. Through the smart phone app, participants see personalized information regarding their monetary reinforcement earned. Study coordinators can monitor validity and compliance on a daily basis and offer feedback to ongoing participants regarding compensation. For the first three days after a quit attempt, participants are paid $5 for transmitting a video demonstrating abstinence, and are paid a bonus if both videos in one day suggest abstinence. After that three day period, participants are paid $2.50 for the the subsequent video, and an escalating amount ($0.10) for each abstinence reading. After 10 successive abstinent readings, participants are paid a bonus of $5.00. Table 2 provides an example of compensation from mCM for a person who has a completely successful first quit attempt. Table 3 provides an example of a participant who has lapses to smoking and switches medications. Participants can earn a

maximum of $585.75 for abstinence (and video compliance) but the average in the pilot of 22 PTSD participants was $300 (Hertzberg et al., 2013).

Table 2. Example Payment Schedule for Successful Quit Attempt

	Days Pre Quit	1st CO	2nd CO	Bonus	Total
Practice Weeks	1 to 21	$1.00			$21.00
	Days Post Quit	**1st CO**	**2nd CO**	**Bonus**	**Total**
Week 1	1	$5.00	$5.00	$5.00	
	2	$5.00	$5.00	$5.00	
	3	$5.00	$5.00	$5.00	
	4	$2.50	$2.60		
	5	$2.70	$2.80	$5.00	
	6	$2.90	$3.00		
	7	$3.10	$3.20		up to $72.80
Week 2	8	$3.30	$3.40		
	9	$3.50	$3.60		
	10	$3.70	$3.80	$5.00	
	11	$3.90	$4.00		
	12	$4.10	$4.20		
	13	$4.30	$4.40		
	14	$4.50	$4.60		up to $60.30
Week 3	15	$4.70	$4.80	$5.00	
	16	$4.90	$5.00		
	17	$5.10	$5.20		
	18	$5.30	$5.40		
	19	$5.50	$5.60		
	20	$5.70	$5.80	$5.00	
	21	$5.90	$6.00		up to $84.90
Week 4	22	$6.10	$6.20		
	23	$6.30	$6.40		
	24	$6.50	$6.60		
	25	$6.70	$6.80	$5.00	
	26	$6.90	$7.00		
	27	$7.10	$7.20		
	28	$7.30	$7.40		up to $99.50
Week 5 & 6	29-42	up to $25 each week			
TOTAL POSSIBLE mCM PAYMENT					**up to $388.50**

Note: Cumulative column indicates payment for videos only (baseline monitoring) and payment accrued for continuous abstinence to that point.

In the first three days of the intervention, CO readings that are a proportion of the individual's baseline value will be used to indicate abstinence (Lamb, Morral, Kirby, Iguchi, & Galbicka, 2004; Lamb et al., 2007). Evidence suggests that by reinforcing gradually lower breath CO levels, a high proportion of breath CO levels less or equal to 6 ppm can ultimately be reached (Lamb et al., 2004). Subsequent to the first three days, CO readings less than or equal to 6 ppm will be used to indicate abstinence from smoking.

C.9.3. Smoking Cessation Counseling. Current clinical practice guidelines (Fiore et al., 2000) recommend the provision of smoking cessation counseling, and most medication trials for smoking cessation in smokers with schizophrenia have included a behavioral counseling component (Tsoi, Porwal, & Webster, 2010). The content of the manual and workbook were adapted from the manual used in the large scale PTSD smoking cessation trial on which the PI was a co-investigator (McFall et al., 2010), and was tailored to the current population based on consensus based clinical practices and our own experience conducting cognitive-behavioral telephone counseling with patients with psychiatric disorders including schizophrenia.

Because participants with psychotic-spectrum disorders may find it difficult to develop therapeutic rapport with telephone counselors, we would like to have two of the counseling sessions occur in-person. We believe that in-person visits (at Session 2 and Session 4) will enhance development of the therapeutic relationship. Because our participants often have difficulty with transportation, we will allow participants to choose to have the visit in our offices, at a local clubhouse, or at their home. If none of these options is reasonable for the participant, he/she will be allowed to participate in these sessions as telephone "visits."

If any participant has a lapse to smoking and chooses to reset a quit date, the study therapist will repeat the content of counseling sessions 2 and 3 instead of progressing to sessions 4 and 5. These sessions may be repeated up to twice each, so that the total number of counseling sessions is capped at nine. Only the first occurrence of Session 2 will occur in the participants' home as described above.

Table 3. Example Payment Schedule for Participant with Difficulty Quitting & Medication Change

	Days Pre Quit	1st CO	2nd CO	Bonus	Total
Practice Weeks	1 to 21	$1.00			$21.00
Week 1	1	$5.00	$5.00	$5.00	
	2	$5.00	$5.00	$5.00	
	3	$5.00	$5.00	$5.00	
	4	$2.50	$2.60		
	5	$2.70	$2.80	$5.00	
	6	$2.90	missed		
	7	missed	missed		up to $63.50
Pt. has lapse to smoking, stops bupropion and NRT, has one week wash-out period, then begins varenicline. After one week on varenicline, pt. has second quit attempt. During two week-period, pt. continues practice mCM.					
	Days Pre Quit	**1st CO**	**2nd CO**	**Bonus**	**Total**
Practice Weeks	1 to 7	$1.00	$1.00		$14.00
Week 1	1	$5.00	$5.00	$5.00	
	2	$5.00	$5.00	$5.00	
	3	$5.00	$5.00	$5.00	
	4	$2.50	missed		
	5	missed	missed		up to $47.50
Pt. has lapse to smoking. Pt. resets quit date for next day.					
Week 1	1	$5.00	$5.00	$5.00	
	2	$5.00	$5.00	$5.00	
	3	$5.00	$5.00	$5.00	
	4	$2.50	$2.60		
	5	$2.70	$2.80	$5.00	
	6	$2.90	$3.00		
	7	$3.10	$3.20		up to $72.80
Week 2	8	$3.30	$3.40		
	9	$3.50	$3.60		
	10	$3.70	$3.80	$5.00	
	11	$3.90	$4.00		
	12	$4.10	$4.20		
	13	$4.30	$4.40		
	14	$4.50	$4.60		up to $60.30
Week 3	15	$4.70	$4.80	$5.00	
	16	$4.90	$5.00		
	17	$5.10	$5.20		
	18	$5.30	$5.40		
	19	$5.50	$5.60		
	20	$5.70	$5.80	$5.00	
	21	$5.90	$6.00		up to $84.70
Week 4	22	$6.30	$6.40		
	23	$6.50	$6.60		
	24	$6.70	$6.80		
	25	$6.90	$7.00	$5.00	
	26	$7.10	$7.20		
	27	$7.30	$7.40		
	28	$5.00	$5.00		up to $109.50
Week 5 & 6	35-42	up to $25 each week			
				TOTAL POSSIBLE mCM PAYMENT	**up to $585.75**

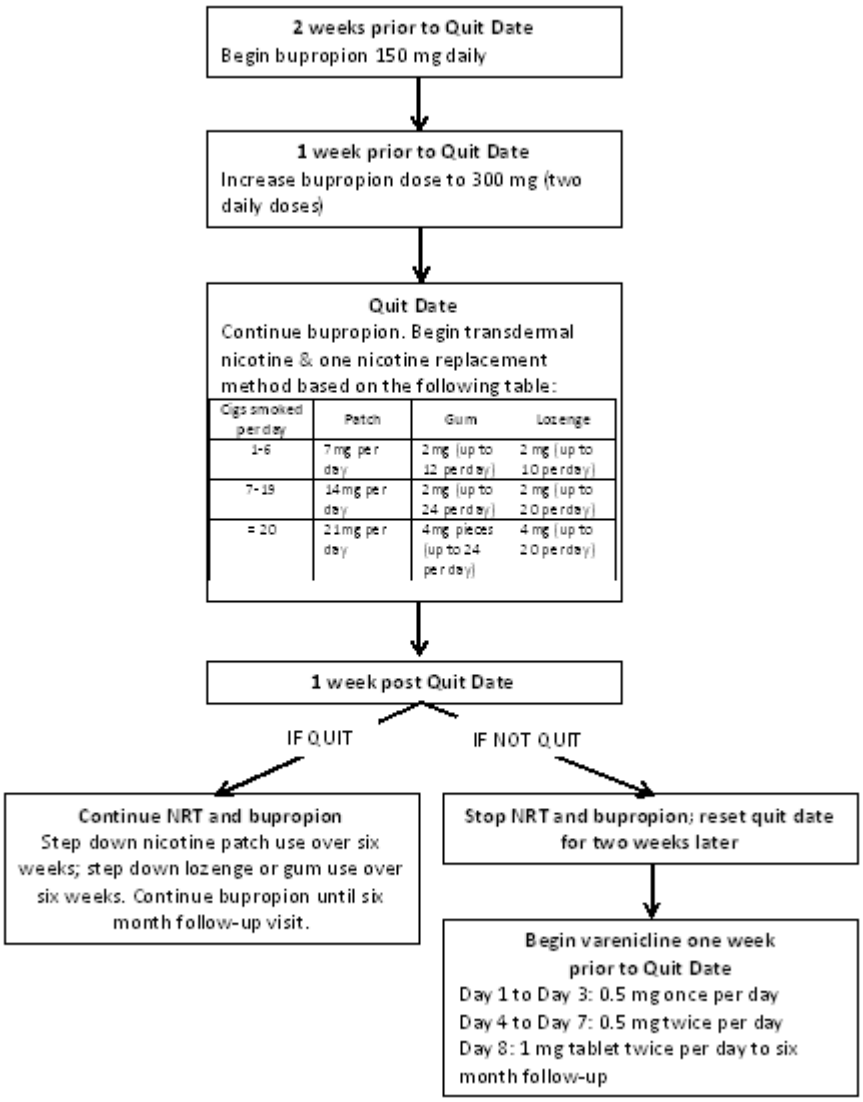
The counseling intervention will be provided to participants by trained masters' level clinicians. All clinicians will attend a half-day training meeting, during which they will be trained by a Ph.D. level staff psychologist with specialized training in behavioral change psychology. Clinicians providing counseling will attend weekly group supervision meetings with the PI and treatment refinement team to listen to audio recordings and review critical points in counseling sessions, discuss cases, and receive ongoing consultation. During Stage 1 (Refinement of Intervention Materials) all counseling sessions will be audio-recorded using an ICD PX333 Digital Voice Recorder. Audio recordings will be transferred to the Duke secured server via direct connection. Recordings will be maintained on the Duke secured server in accordance with Duke's Retention of Records Policy, i.e., for six years after the study has been closed. During Stage 2, (RCT) a random selection of 20% of all counseling sessions will be recorded and a doctoral level clinical psychologist (Dr. Calhoun) will rate counselor treatment fidelity/adherence using the Yale Adherence and Competence Scale system (YACS; Carroll, 2000). The system includes checklists for measuring critical treatment elements and counselors will receive fidelity feedback.

C.9.4. Smoking Cessation Aids. Figure 1 summarizes the smoking cessation aids used in the study. There is good evidence that bupropion is associated with increased quit rates compared to placebo for smokers with schizophrenia (Tsoi, Porwal, & Webster, 2010). All participants (for whom it is not contraindicated; see Section C.10.) will be prescribed bupropion, which they will start two weeks prior to their quit day [150 mg/daily for days 1-7 and 300 mg/daily (administered in two daily doses) until the 6-month follow-up].

Because bupropion has been shown to improve quit rates at posttreatment and at 6 month follow-up in smokers with schizophrenia (Tsoi, Porwal, & Webster, 2013), participants will continue bupropion until the 6 month follow-up**.** Because bupropion cessation is not typically associated with withdrawal symptoms, participants will not be required to taper use

(Moore, personal communication). Anthenelli and colleagues (2016) suggested varenicline use may increase rates of abstinence over bupropion use. In that study of smokers with psychiatric disorders and without, use of varenicline was not associated with increased risk of moderate to severe neuropsychiatric adverse events relative to nicotine replacement therapy or placebo among smokers with and without psychiatric disorders. Participants who have been unable to quit or have relapsed to smoking within five to seven days of their quit date (as evidenced by three missed or positive CO readings in a row) will be asked to use varenicline. A one-week washout period (mean half-life of bupropion SR is 21 (±9) hours) will occur between the stopping of bupropion and the starting of varenicline. Participants will not be prescribed varenicline if they have been able to maintain abstinence with use of bupropion and NRT.

Figure 1. Pharmacotherapy Protocol Flowchart



Any participant who has a lapse to smoking but does not wish to use varenicline will be allowed to set a new quit date for the following day without switching medications. Participants will be able to reset a quit date twice within the first fifteen days after their initial quit date.

In order to track adherence to bupropion or varenicline use, participants' medication bottles will be fitted with Medication Event Monitoring System (MEMS) 6 TrackCap bottle caps that measure the date, time, and dose of medication administration. At each in-person visit, participants will be asked to bring their medication with the MEMS cap, and the study coordinator will upload data from the cap to the Duke secured server using a USB connection. Additionally, participants will be asked to keep all study medication bottles, including those that are empty, and bring the bottles to the end-of-treatment (Session 7) visit so that we can further evaluate medication compliance.

Although there is little evidence that NRT alone improves long term abstinence rates for smokers with schizophrenia (Tsoi, Porwal, & Webster, 2010), we have chosen to include it as part of our multi-component treatment. NRT is recommended as a first line treatment in clinical practice guidelines (Fiore et al., 2000) and theoretically could minimize potential effects of nicotine withdrawal on neurocognitive functioning (e.g., sensorimotor gating) in smokers with schizophrenia (Ziedonis et al., 2008). Smokers will be prescribed the NRT patch and one nicotine rescue method (e.g., nicotine gum, lozenge). Because the polycyclic aromatic hydrocarbons of tobacco smoke can affect the metabolism of some antipsychotic medications (e.g., olanzapine, clozapine, haloperidol, fluphenazine), resulting in reduced medication blood levels (Fiore et al., 2000), patients will be closely monitored for increased medication side effects during the trial.

C.9.5. Rationale for Text Messages to Increase Smoking Cessation Medication Adherence. Many patients, including those with schizophrenia, are not completely adherent with their medications, and they may benefit from text message reminders. Patients commonly indicate that ahead of side effects or lack of interest, missed doses are due to forgetting

or being busy, being away from home, and changes in daily routine (Tuldra et al., 1999). Adherence with smoking cessation medications is associated with higher quit rates (Hollands, Sutton, McDermott, Marteau, & Aveyard, 2013; Shiffman, Sweeney, Ferguson, Sembower, & Gitchell, 2008). Text messaging may increase medication compliance, as suggested by a recent Cochrane Review finding mobile phone text-messaging to be efficacious for adherence to HIV medications (Horvath, Azman, Kennedy & Rutherford, 2012). There is evidence that weekly text messages for medication adherence may be more effective than daily reminders even though most medications are taken daily (Pop-Eleches et al., 2011).

C.9.6. Quitbit. Participants will be provided with a Quitbit Lighter, http://www.quitbitlighter.com/. This lighter tracks when and how often a participant lights a cigarette. The Quitbit communicates with smart phone devices via Bluetooth connectivity. The smartphone application (https://itunes.apple.com/us/app/quitbit-quit-smoking-cigarettes/id864129396?mt=8) includes charts and graphs of smoking patterns, a social media component, and resources for smoking cessation and requires an account for logging in. Participants will be provided false accounts the purposes of the study. Information regarding patterns of smoking will be useful because it can help patients identify situations that might increase risk of smoking or relapse. Because of the privacy risks inherent in use of the social media component of the app, we will advise participants not to participate in this portion of the app. There is an app setting that allows other users of the social media site to see participants' smoking patterns; we will set this to "no" for all participants, and we will advise participants not to change any settings within the app. Any participant who does not wish to use the Quitbit lighter will not be required to do so.

C.10. Participants, Screening and Recruitment

The inclusion criteria for Stage 1 and Stage 2 studies are the same, and are as follows:

Participants must meet **all** inclusion criteria:

- Currently smoke at least ten cigarettes a day
- Have been smoking for at least one year
- Meet criteria for schizophrenia, schizoaffective disorder, or another psychotic disorder based on structured clinical interview
- Can speak and write fluent conversational English
- Are between 18 and 70 years of age
- Are willing to make a smoking cessation attempt
- Score 16 or higher on the Montreal Cognitive Assessment

Participants who meet **any** one of the exclusion criteria will be excluded:

- Have a history of myocardial infarction in the past 6 months
- Have a contraindication to NRT with no medical clearance from the primary care provider or study physician
- Use and unwillingness to stop use of other forms of nicotine such as cigars, pipes, or chewing tobacco
- Are pregnant
- Meet criteria for a current manic episode based on structured clinical interview
- Are currently enrolled in another smoking cessation trial
- Are currently imprisoned or in psychiatric hospitalization

Prior to study entry, potential participants will complete a screening/baseline visit, in which informed consent will be obtained and a breath sample to assess CO level will be taken. Urine samples will be obtained to screen for illicit drug use and to obtain cotinine levels. Because urine will already be collected at the screen to document drug use, urine samples will be acquired and assayed using semi-quantitative test strips (Accutest; Jant Pharmacal Corporation, Encino, CA). Because urine drug screen results are not exclusionary, but rather provide descriptive information about the study population, any participant may refuse to provide a urine sample for drug screen purposes. We have not added this caveat to the informed consent form because we want to encourage participants to provide the urine samples. At any time, if a participant refuses to provide a urine sample, this will be documented as a protocol deviation. Of note, to date we have had no participants in studies in the Traumatic Stress and Health Research Laboratory refuse to provide a urine sample for drug screening. Because the study drugs are each Category C drugs, urine pregnancy tests will also be completed for women of childbearing potential. We have developed a short interview for female participants; this

interview will help us determine which female participants must have a urine pregnancy test, and when the test should be done. Female participants of childbearing potential who are not pregnant must agree to use appropriate contraception during the course of the study, and to notify study staff if they become pregnant during the study.

Medical Clearance: Participants will be screened for good health via self-report. If any participant indicates that he/she has a primary care provider and/or other treating physician, medical clearance to participate in the study will be obtained from that care provider (see letter to physician). If the request is denied, potential participants will be excluded from the study. If the request is not returned within two weeks, the study physician will determine eligibility. We are seeking medical clearance rather than excluding participants based on self-report to ensure that we are not prematurely ruling out participants who may be eligible. We are consulting with their primary physician to determine if the use of nicotine replacement therapy is appropriate and safe given their current physical status and medication regimen. Because bupropion use is contraindicated in persons with seizure disorder and/or uncontrolled diabetes, we will specifically indicate these diagnoses in the notification to physicians. This medical consult is a way to further protect the participant and also give them an opportunity to take part in the study if their physician deems it appropriate and safe. All participants who are medically eligible will also be prescribed bupropion (or varenicline monotherapy if he/she fails to quit while using bupropion). If a participant with a seizure disorder, history of or current hepatitis and/or cirrhosis, renal impairment, and/or uncontrolled diabetes wishes to enroll in the study, he/she will not receive contraindicated medications. If a participant with any of these medical conditions is unwilling to participate in the study without taking bupropion or varenicline, he/she will be withdrawn from the study.

Table 4: Study Baseline and Outcome Measures

	Items	Month			
		0	PT*	3	6
BACKGROUND VARIABLES					
Demographics	31	X			
Structured Clinical Interview	-	X			
Smoking history/Current smoking	5	X			
Smoking motives/consequences	76	X			
Reasons for quitting	20	X			
Cell phone use questionnaire	9	X		X	X
Nicotine dependence scale	6	X	**X**	**X**	**X**
Drug Abuse Screening Test	20	X			
Alcohol Use Disorders Identification Test	10	X			
Montreal Cognitive Assessment	8	X	**X**		**X**
Calgary Depression Rating Scale	9	X	**X**	**X**	**X**
Positive symptom scale (SAPS)	31	X	**X**	**X**	**X**
PTSD Checklist	25	X		**X**	**X**
CAINS	13	X	**X**	**X**	**X**
Readiness to change measure	3	X	**X**	**X**	**X**
Readiness & motivation to change	10	X			
Intolerance for Smoking Abstinence Discomfort	17	X	X	X	X
NRT Contraindications	2	X			
Global self-efficacy	1	**X**	**X**	**X**	**X**
Social Support	1	**X**	**X**	**X**	**X**
Questions about CO monitoring	5		X		
Cessation knowledge measure	20	X	X		
PROCESS MEASURES					
Smoking cessation aids	4	X	X	X	X
Adherence measure	8		X		
Treatment acceptability measure	8		X		
Treatment feasibility measure	8		X		
Intervention	3		X	X	X
OUTCOME MEASURES					
Efficacy: Prolonged Abstinence; 7-day; 30-day abstinence	9		X	X	X
Quit Attempts	2		X	X	X
Time-line Follow-Back-Quit Attempts			X	X	X
Yale Adherence measure	-		X		

***Post-treatment; Bolded X denotes the revised administration schedule of measures.**

C.11. Recruitment, Study Setting, and Informed Consent

We aim to have a total of 51 study completers, and we estimate that we will need to consent and screen up to 75 participants to reach that goal. To ensure a representative sample, we will recruit from the UNC outpatient STEP clinic that specifically treats patients with severe mental illness (n = 630), 60% of whom are diagnosed with schizophrenia. We

will also recruit from "clubhouses," recovery oriented programs that assist adults with severe mental illness to stay out of the hospital, succeed at work, advance their education, and reach their goals. Four area recovery area clubhouses will be the recruitment sites from which smokers with schizophrenia will be identified. Each of the clubhouses has approximately 100 individuals with schizophrenia who are regular participants at the clubhouse (n = 400). Based on an 80% prevalence rate of smoking, we expect almost 600 smokers with schizophrenia will be eligible to participate in the study, and that we will be able to meet the recruitment goal of enrolling 15 smokers with schizophrenia in the successive cohorts (Stage 1) and 36 smokers with schizophrenia in the RCT pilot (Stage 2). In order to reach any smokers with schizophrenia who are not members of local area clubhouses, we will also advertise the study at www.craigslist.com.

Potentially eligible participants will be identified using Duke's DEDUCE and Maestro systems. We will contact the clinical provider of any potentially eligible participant to inquire about eligibility. If the clinical provider believes that his/her patient would be potentially eligible, we will provide the provider with a recruitment letter to give to his/her patient at a future appointment. The recruitment letter will describe the study, and provide an "opt-out" option if the potential participant does not wish to be contacted further by the research staff. About one week after the potential participant is given the letter by his/her provider, a study team member will contact him/her by phone to discuss participation (see IRB-approved phone script).

Our study team will use social media to reach potentially eligible participants. We have developed a Facebook page for posting IRB-approved study flyers and information for this and other studies in the Traumatic Stress and Health Research Laboratory, https://www.facebook.com/Duke-Traumatic-Stress-and-Health-Research-Lab-379366159145563/. We plan to place pictures of our study flyers on the Facebook page, and use Facebook's post boost to draw attention to the post. The post itself will say "Enroll now!" or "Now enrolling!" We will also plan to use Facebook ads to target potential participants within a 50-mile radius of Duke. The proposed Facebook ad photos and text have been uploaded to the recruitment materials section of the eIRB space. If any participant contacts the email associated with the Facebook page (TSHRLab@dm.duke.edu, he/she will be sent an automatic email response.

Any participant who contacts by telephone the study coordinator or other study staff regarding the study will be provided more information, and will be interviewed using an IRB-approved telephone screening. The telephone script that is used for this purpose contains many of the required elements of consent.

Transportation to and from Duke University Medical Center may be difficult and cost-prohibitive for potential study participants. In order to facilitate enrollment and treatment for smoking cessation, the administrative officers of two local area clubhouses, Club Nova in Carrboro, NC and Threshold in Durham, NC, have indicated that they will allow our study staff access to private rooms and/or offices at their facilities for screening, treatment, and follow-up visits. Similarly, staff members with local area assertive community treatment (ACT) teams have indicated that their participants may prefer to be seen in the community, and they have allowed staff access to space for completing screening, treatment, and follow-up visits, in case that easier for participants. This option will be made available to potential participants who receive services at these respective facilities. Finally, if any participant wishes that his or her post-treatment and/or follow-up visits occur in his/her home, study staff will travel for those appointments. See ***C.15.4 Risks Associated with Community Visits,*** for more information on safety planning for community visits.

Once a participant reports to the laboratory or is visited in the community to begin the study, the study staff member obtaining consent will explain the study in detail, provide the participant with an IRB-approved written consent form explaining the procedures and risks, and answer any questions. The initial consent process and documentation takes place in a quiet, private office in Dr. Beckham's research laboratory or in a private office or room at Club Nova or Threshold. Participants are given the chance to thoroughly read the consent prior to participation. Participants are given a copy of the signed informed consent form, and are given phone numbers to call if they have additional questions about the consent form or the research, if they have any problems during the study, or if they have questions about participating in research studies in general. With regards to determination of decision making capacity of potential participants, our laboratory has a standard procedure for determining understanding of the study procedures, risks, and benefits. We utilize this procedure if we have any reason to suspect that the participant may have difficulty in the consent process (e.g., traumatic brain injury impacting cognitive function, active psychotic symptoms). In this procedure,

the study coordinator providing the informed consent information evaluates understanding of the procedures at several different time points during the process by asking questions like "Do you understand what we're asking you to do?" and "Do you have any questions about the risks of the study? Can you tell me what you understand the risks to be?" Prior to having a participant sign consent, the study coordinator, who has clinical experience in working with persons with psychotic disorders, may ask the potential participant to outline the study procedures, risks, and benefits so that he can make sure that the participant is aware of them. If the participant is unable to summarize these, he/she will not be allowed to sign the informed consent form, and may be referred for other treatment. No study procedures will begin until informed consent has been obtained.

C.12. Measures

We have experience with all the proposed measures and items discussed below (see also Table 4). The diagnostic assessment and baseline questionnaires will take about 4 hours, and this is typical of many of our smoking cessation studies that include homeless smokers and smokers with schizophrenia. The process and outcome measures will be administered at post-treatment and follow-up and take about 30 minutes to complete. Stage 1 will assist in determining the feasibility of the assessment and also indicate measures that may be unnecessary.

C.12.1 Demographic and Diagnostic Measures. Age, race, gender, marital status, education, employment status, travel time, cell and smart phone use will be collected from each participant. The presence of mood disorders and/or psychotic spectrum disorders will be evaluated using the Structured Clinical Interview for DSM-IV Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1996) or the SCID5 when it becomes available. Emerging research suggests that comorbid physical health ailments, especially autoimmune diseases, increase the risk of mortality for individuals with schizophrenia, in particular smokers (Dickerson et al., 2016). We will gather a brief medical history from participants to be used in describing the study population.

***C.12.2. Cognitive Functioning*.** The Montreal Cognitive Assessment (MoCA; Freitas, Simoes, Maroco, Alves, & Santana, 2012) is a well-validated screen of cognitive functioning, showing excellent criterion validity in psychometric validation studies. Administration time is 5-10 minutes and measures attention, executive function, verbal memory, language, abstraction, and orientation.

C.12.3 Smoking Related Measures. The Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1996) and a general smoking history questionnaire (e.g., number of cigarettes smoked/day, age of first smoking, number of previous quit attempts, living with a smoker) will be used to measure smoking behaviors. Participants will be asked to respond to several questions to determine if he/she has contraindications to receive NRT. If any contraindications are found, the participant must receive study physician approval prior to receiving NRT.

Contraindications for bupropion will be assessed by the study physician. Participants will complete measures designed to examine motives for smoking, reasons for quitting, and smoking consequences. The Smoking Motives Questionnaire (Russell, Peto, & Patel, 1974) is designed to measure the smoking motivation in several domains, including psychosocial, sensorimotor, and addictiveness. The Reasons for Quitting Scale (Curry, Wagner, & Grothaus, 1990) is designed to capture the intrinsic and extrinsic motivators of smoking cessation. It includes 20 items that measure the dimensions of health concerns, self-control, immediate reinforcement, and social pressure. The Smoking Consequences Questionnaire-Adult (Copeland, Brandon, & Quinn, 1995) is a 55 item questionnaire that measures the positive and negative expectancies of smoking of experienced, nicotine-dependent smokers. The Intolerance For Smoking Abstinence Discomfort scale (Sirota, Rohsenow, MacKinnon et al., 2010) is a 17-item scale measuring smokers' ability to discomfort specifically related to abstinence from smoking.

C.12.4 Psychiatric Symptom Measures. The Calgary Depression Rating Scale (CDRS) will assess depressive symptoms. The CDRS has been shown to be reliable in patients with schizophrenia (Addington, Addington, Maticka-Tyndale, & Joyce, 1992). The Scale for the Assessment of Positive Symptoms (SAPS) will measure severity of positive symptomatology in patients with schizophrenia or schizoaffective disorder, and the Clinical Assessment Interview for Negative Symptoms, or CAINS, will be used to measure negative symptoms. The SAPS assesses hallucinations, delusions, bizarre behavior, and positive thought. Reliability and validity for the SANS is good (Andreason, 1982; Andreason, Arndt, Miller, Flaum, & Nopoulos, 1995), and the CAINS has shown good internal consistency and interrater agreement and

strong convergent validity (Kring et al., 2013). Self-reported alcohol use will be assessed with the ten-item Alcohol Use Disorders Identification Test, or AUDIT (Bradley & Bush, 1998). Substance use will be assessed with the Drug Abuse Screening Test (DAST; Skinner, 1982). Given the high rates of trauma and posttraumatic stress disorder (PTSD) among persons with psychotic disorders (Neria et al., 2002), we will examine PTSD symptoms at the screening and 3- and 6-month follow-up visits using the PTSD Checklist 5 (PCL5; Weathers et al., 2013).

C.12.5. Self-Efficacy, Readiness to Change and Social Support. A single item ("How confident are you that you will be able to quit smoking?" 1= Not at all confident to 4= Very confident) will be used to measure global self-efficacy for quitting smoking (Shiffman et al., 2000). The use of a global measure of SE is supported by previous studies in which multiple-item SE questionnaires formed a unifactorial construct (Baer, Holt, & Lichtenstein, 1986). The Readiness to Change Questionnaire (RCQ; Rollnick, Heather, Gold, & Hall, 1992), which is designed to assess attitudes toward quitting smoking (Heather, Rollnick, & Bell, 1993), will be administered at baseline. Additionally, readiness, motivation and confidence to change smoking behaviors will be measured using an 11-item scale (Crittenden et al., 1994) at baseline. Self-efficacy for taking NRT and bupropion as prescribed will be assessed on a 10-point Likert Scale. Social support will be assessed using a single item used in the NIH PROMISE study (Williams, et al., 1992). The item is "Do you have someone you feel close to, someone you can trust and confide in?"

C.12.6. Delay Discounting. Delay discounting will be assessed by a laboratory task administered at baseline and at the 6-week follow-up (6-weeks post-quit date). Participants will complete the computerized delay discounting task for hypothetical monetary values. They will choose between a fixed amount with fixed delay and various monetary amounts available immediately (Garcia-Rodrigquez, Secades-Villa, Weidberg, & Yoon, 2013). Delays and monetary options will be presented in ascending order and adjusted with procedures that successively approximate an indifference point.

C.12.7. Smoking Cessation Counseling Fidelity. As used in our prior studies (e.g. McFall et al., 2010), we will utilize a revised version of the Yale Adherence and Competence Scale (YACS) system to measure counselor adherence in delivering behavioral treatments for substance abuse disorders (Carroll, 2000). The system includes checklists for measuring critical treatment elements. A random selection of 20% of the counseling sessions during the RCT will be recorded and rated by Dr. Calhoun for counselor fidelity/adherence. Fidelity feedback will be provided to the counselor(s).

C.12.8. Measures of Treatment Acceptability. Patient's satisfaction with the intervention will be assessed with survey items at the end of each treatment session during Stage 1 and at the end of treatment in the Stage 2 RCT. These items will assess: 1) reactions to the topics discussed and skills reviewed; 2) comfort with the therapist; 3) opinions of the materials used in session and homework (e.g., participant workbook); 4) overall satisfaction with the intervention at that point in time; and 5) comfort with the mCM app and texting (for those assigned to iCOMMIT only). Upon completion of the intervention, patients will complete an exit questionnaire that includes both Likert-type items and open-ended questions to assess what they liked and disliked about the intervention, their thoughts about the duration and number of sessions, topics covered, perceived benefits of their participation, comfort level, overall satisfaction, and suggestions for improvement.

C.12.9. Measures of Treatment Feasibility and Adherence. Feasibility of the intervention will be evaluated in part *via* protocol fidelity monitoring (as described in *C.9.3. Smoking Cessation Counseling*). Intervention feasibility will also be evaluated *via* weekly questionnaires completed by therapists. Items will assess therapists' perceptions of 1) the feasibility of completing the planned material in the manual for that particular session in the allotted time; 2) the appropriateness of the topics reviewed; and 3) their patient's perceived responses to the material. Open-ended questions will be included to capture therapists' suggestions for improving session content and process. These items will be reviewed weekly in supervision with Drs. Beckham and Calhoun.

Feasibility of patient retention will be assessed by detailed tracking of attendance at each treatment session. Measures will include number of counseling sessions completed, the number of missed or cancelled appointments, and the proportion of patients who withdraw/drop-out or are lost to follow-up. Participants who withdraw from treatment will be contacted to elicit feedback on their reasons for dropping out. Feasibility of the use of the mHealth applications will be assessed by tracking: 1) the proportion of required videos uploaded using the mCM app; 2) information regarding lost

or stolen cell phones; and 3) participants' use of and comfort with the mHealth apps at the beginning and end of the intervention. We will also assess the number of participants who have a) mobile smart phones and b) unlimited texting at the time of enrollment (which will inform budgeting for a larger trial).

Medication adherence to NRT and bupropion will be assessed. Individuals who were optimally adherent were found to be more than twice as likely (52%) to be abstinent at 6 months than were those with lower adherence (25%; Catz et al., 2011). Optimal adherence will be defined as using $\geq$ 80% of their NRT and bupropion. The primary self-report measure of adherence will be the number of days NRT (and bupropion if prescribed) are used during the study period. Participants will also complete the Morisky Adherence Questionnaire (Morisky, Green, & Levine, 1986; Toll, McKee, Martin, Jatlow, & O'Malley, 2007). This 8-item questionnaire is a general adherence measure that produces unintentional and purposeful non-adherence subscales. The questionnaire has been validated with smokers as an adherence screening measure (Morisky, Green, & Levine, 1986; Toll, McKee, Martin, Jatlow, & O'Malley, 2007) and as a post-treatment measure of adherence (Catz et al., 2011). Days of medication use will be recorded at each treatment visit and follow-up [during treatment, post-treatment and 3 months (for bupropion)].

C.12.10. Smoking Cessation Outcome Measures and Biochemical Verification. Our choice of primary and secondary smoking endpoints follows recommendations by the Society of Research on Nicotine and Tobacco (SRNT; Hughes, 2003). Self-reported and bio-verified prolonged abstinence at the 6-month follow-up will be the primary end-point. Prolonged abstinence will exclude tobacco use in the first two weeks following the quit date Hughes et al., 2003). Self-reported prolonged abstinence will be verified by cotinine assay. Saliva samples will be collected from participants who report prolonged abstinence at each follow-up. Saliva samples will be sent to the Duke University Nicotine Research Program to be analyzed for the presence of cotinine using a standard cut point of 10 ng/ml to determine abstinence. A blind sample of 5% will be rerun to assure test accuracy of saliva samples. Secondary smoking outcomes will include 7- and 30-day point prevalence abstinence at each assessment, where abstinence is defined as no tobacco use in the prior 7 or 30 days respectively. Additionally, participants will be asked if they have made one or more quit attempts in each follow-up period using a time-line follow back method (Lewis-Esquerre et al., 2005). We have recent experience using this method to assess daily smoking behavior.

C.13. Participant Reimbursement

Participants will receive partial reimbursement for the time they donate. Participants will receive $100 for screening evaluation and mCM training. This payment will be paid to any participant who is determined to be ineligible at the screening session. The maximum total compensation available through mCM is $513.50. Participants are not reimbursed for attending counseling sessions. Participants will be paid $25 for providing a CO reading at session 7, the end-of-treatment visit. Based on our experience in our previous smoking cessation projects, we are adding a $75 incentive for completing each follow-up, including $25 for completion of the follow-up questionnaires and $50 for providing a saliva sample that indicates abstinence if abstinence is reported during the interview. We are using these incentives in our other smoking cessation treatment trials with success. To enhance abstinence at the 3-month follow-up visit, any participant whose CO readings indicate abstinence at that visit will be paid an additional $100. To ensure that participants return the smart-phone, we will provide postage paid return mailers and are adding an additional $50 incentive upon receipt of the phone at Session 7. In order to enhance rates of equipment return, any participant who doesn't return the loaned study phone will have their final payment decreased by $100. Total compensation for full participation (and abstinence) is $938.50. Participants assigned to the control group in Stage 2 will be paid up to $375 for full participation (and abstinence).

C.14. Risk/Benefit Analysis

C.14.1 Risks. The clinical interview to establish diagnosis can cause some psychological distress in the form of a temporary increase in anxiety, but any ensuing distress is usually well tolerated. There are no known psychological hazards or risks associated with completing questionnaires or electronic diaries.

Quitting smoking will cause nicotine withdrawal that may lead to headaches, nausea, irritability, weight gain, difficulty concentrating, poor sleep, increased appetite, anxious or depressed mood, and craving for cigarettes. Participants will be asked to use nicotine replacement therapy (NRT). There are therapeutic risks associated with the use of NRT. Minimal

risks associated with wearing a nicotine patch include skin irritation, dizziness, lightheadedness, increased heart rate or blood pressure, nausea or vomiting.

Risks of bupropion use include dry mouth, insomnia, nausea, constipation, headache, shakiness or jitteriness, skin rash, sweating, allergic reaction, change in appetite, weight loss, dizziness, tremor, thinking abnormally, hot flashes, worsening depression or suicidal thoughts and behavior, and ringing in the ears. At the highest dosage of bupropion to be used in this study, seizures occurred in 1 out of every 1000 (0.1%) who took this drug. Participants are informed that they are not required to take bupropion, and will be allowed to participate in the study if they refuse to do so.

Risks of varenicline use include neuropsychiatric symptoms and suicidality, seizures, new or worsening cardiovascular problems (mostly in people who already have cardiovascular problems), accidental injury, sleep walking, skin reactions including rash, swelling, redness or peeling, nausea, sleep problems, constipation, gas, vomiting, worsening depression, agitation.

There is a research risk associated with the loss of confidentiality of study data. Specifically, collection and transfer of videotaped carbon-monoxide monitoring have risks with regards to privacy and confidentiality. Please see "Protection From Risk: Data Security" for details on reduction of risk with regards to the proposed videotaping. In addition, there is a risk of reduced privacy and/or confidentiality associated with community and/or home visits for care. In order to reduce risk of loss of privacy or confidentiality, we will transport all study data, including informed consent forms for the first visit, in a locked briefcase. Data collected via computer will be collected on a password-protected laptop for which only study staff members have the password. Finally, we will only provide community visits to participants when a private office or room is available for study visits. When visiting a community site, study staff members will contact the administration at the community site prior to each visit in order to ensure that a private room will be available for use for the duration of the visit. Any potential participant who wishes to have their screening visit and informed consent occur in the community will be warned of the risks to privacy and confidentiality during the telephone screening process.

In order to monitor possible side effects, participants will be instructed to report any side effects as soon as possible to research staff; they will have contact information needed to report these problems to study personnel. At each session following initiation of the nicotine replacement therapy, participants will also be questioned about any side effects to further monitor any adverse reactions. As increased risk of suicide is a potential side-effect of bupropion, at each session after participants have begun use, they will be asked about any increased risk of suicide as compared to baseline. Since our laboratory keeps thorough documentation of baseline suicide risk, this comparison can be easily made. If any increased risk is reported, senior study clinical staff, as identified in the Psychiatric Emergencies Standard of Practice, will be notified and a thorough suicide risk assessment will be performed.

Adverse events, serious adverse events, and unanticipated problems will be reported to the Duke IRB in accordance with IRB guidelines.

C.14.2.Benefits. While participants may benefit from quitting smoking, there are no guaranteed benefits to the individual participants and no immediate benefits of the proposed research to others. There are potential benefits to others from the information generated that potentially will be helpful in increasing reach of smoking cessation and developing more effective treatment interventions for smoking cessation in smokers with schizophrenia. In our opinion, the anticipated benefits of this study outweigh the potential risks.

C.15. Protection From Risk and Data Security

Risks of participation, interviews, nicotine products , bupropion, and varenicline are described in the consent form. Potential risks will be minimized by carefully screening participants according to the inclusion/exclusion criteria, closely monitoring symptom levels, and following established laboratory procedures. Quitting smoking should enhance rather than jeopardize health status, and potential serious adverse events (SAE) for participants in this project are not expected. Regardless, we will minimize potential risk by careful screening of potential participants. Those with contraindications for NRT, bupropion or varenicline will require medical clearance by their primary care provider or they

will not receive study medications. Please see "***C.15.5 Data Safety and Monitoring"*** for additional information regarding risk related to study treatments.

We will be providing the study phones to participants for the course of the study and will retrieve them at the conclusion. We will restrict access to the following applications: Safari, Camera (also disables FaceTime), FaceTime, iTunes Store, iBooks Store2, installation of apps, deletion of apps, in-app purchases, Siri, and AirDrop. We will prevent access to music, podcasts, movies, TV shows, Books2, apps, Siri, and other websites. We will prevent ability to change the following: accounts, FindMyFriends, cellular data use, background app updates, location services, contacts, calendars, reminders, photos, Bluetooth sharing, microphone, Twitter, Facebook, and advertising. We will have the ability to remote wipe the phones if they are not returned. We will encourage participants via consent to only enter information on the phone that they are comfortable with sharing with the entities listed below. If a participant is lost to contact after he/she should have begun home monitoring (defined as two weeks of no contact and no video recordings loaded), we will disable the telephone and telephone service, and will only reinstate service if the participant contacts the laboratory.

C.15.1. mCM Information Security**.** The collection and transfer of videotaped carbon-monoxide monitoring have risks with regards to privacy and confidentiality. The smart phone is programmed such that a staff member will set up the telephone and enter the participant's code into the phone. When the participant chooses to upload a video, he/she uploads the video directly from the phone to a website at InMotion Hosting (see below for further information about the website), and the phone programming ensures that the video is uploaded into the correct participant's area of the website. This ensures that study participants' data is stored in the correct place, and that study participants cannot view any other participants' data. Participants are asked to review their videos before posting, and they can choose not to upload any video that they don't wish to upload for any reason. Data from the CO reading are collected by the smart phone app via electrochemical sensor (i.e., high frequency sound waves), and are transmitted to InMotion Hosting along with the video recordings.

For the study's website, we will use shared server space provided by InMotion Hosting, Inc. The video recordings will be collected on iPhones using iOS7, or on Droid MAXX 2 phones using Android 5.1.1 Lollipop. Each of these operating systems is FIPS-140-2 compliant. InMotion Hosting states that data are AES-256 encrypted at rest, and the data being transferred are encrypted at transfer (AES-256). Data will be unencrypted only by study staff who have access to the secured server at InMotion Hosting; the encryption key is held only by our staff. InMotion states that they run audits regularly of the websites hosted within their shared servers to prevent scriptside vulnerabilities, and the company has a 24/7 support team monitoring their servers. The East Coast data center, which is where our data would be hosted, is located in Washington D.C. in a protected facility with 24/7 security surveillance and identity management. The web application written for this study has been checked by the application developer, Jeffrey Hertzberg, for SQL injection, Code Injection, XSS, and RFI vulnerabilities and has passed. The site will only be accessible by the study participants and the study coordinators via 512-bit SHA-2 hashed passwords.

In previous studies using this methodology that have been run in the Traumatic Stress and Health Research Laboratory, we have had no participant complaints regarding issues of privacy and confidentiality related to use of the smart phone videotaping procedures. As security controls have not been validated for InMotion Hosting, we will include a statement in the informed consent that the data/videos voluntarily submitted will be sent to InMotion and are no longer covered by Duke privacy protections.

C.15.2. Quitbit Information Security. The study staff will load the Quitbit app onto the loaned phones from the iTunes store and will accept the End User License Agreement (EULA). The app requires that an account be created for users; we will create a false account for participants so that their personal information is not used in account creation. The app includes a setting that allows other users of the social media site to see participant's smoking patterns. In order to reduce the likelihood of this happening, we will set this function to "no" upon set up. Participants will be advised not to change settings within the app to decrease risks related to confidentiality and privacy. Also, because of the privacy risks inherent in use of the social media component of the app, we will advise participants not to participate in this portion of the app.

C.15.3. Other Data Security. There are several key personnel outside Duke. The staff are listed as key personnel because they provide technical support (Hertzberg), administrative support (Neal and/or Lee), or support in recruitment efforts at the Durham VA (Carpenter). None of these "key personnel outside Duke" will have access to participants' identifying information or data. Data that links participants to information collected in the course of a given study will be kept separately from identifying information in an electronic, password-protected MS Access database stored at duhsnas-pri\dusom_psych\private\Beckham Logs\iCOMMIT; the key connecting identifying information and data will be stored here as well. Hard copy paper records will be stored in a locked filing cabinet in the study coordinator's locked office, within Dr. Beckham's laboratory space at Duke-leased Hock Plaza. Information from the interview and/or questionnaires may be entered into a computerized database that will be stored on the DUMC server at duhsnas-pri\dusom_psych\private\Beckham Logs\iCOMMIT in a password-protected database separate from the "logbook" of identifying information. This database is accessible only by Dr. Beckham and study staff. Any staff members who leave the study for any reason will have access to study resources, including data, removed immediately.

C.15.4 Risks Associated with Community Visits. Privacy and confidentiality risks and protective measures are described in section C.14.1 herein. With regards to study staff members, there may be risks associated with community visits. We have mitigated the risk of danger associated with study visits in the community by choosing to provide study visits at public locations, and only upon prior approval by administrative teams at those clubhouses. However, in order to further mitigate risks, we have developed a safety checklist and safety tips and guidelines for community visits; see full protocol section of eIRB workspace. These strategies are based on safety guidelines for community workers in the Department of Veterans Affairs (Prevention and Management of Disruptive Behavior, VHA Central Office, 2013). Study staff members will be asked to do the following:

- contact community resource administrative personnel (e.g., management at Club Nova) to ensure space availability;
- use a locked study briefcase for study hard-copy materials;
- carry a charged cell phone at all times;
- email trip itinerary to a senior staff member, and designate a study staff member to be a central contact person for the duration of the visit; and
- Communicate with the central contact by phone regarding arrivals and departures.

Participants who choose to have any community visits occur in their home will be asked to review and sign a safety agreement with the study coordinator. Any participant who chooses to not sign the safety agreement will be required to meet with the study staff members in public community areas or in the laboratory.

C.15.5 Data Safety and Monitoring. The individuals responsible for data safety and monitoring will be the PI, the project coordinator, and the Study Physician. The Study Physician for this trial is Scott Moore, M.D., Ph.D. Dr. Moore is a board certified psychiatrist, and he is Medical Director of the Durham VA Medical Center's Smoking Cessation Clinic. As Study Physician, Dr. Moore will ensure participants are medically cleared to participate in this trial, provide study medications, and review all reports of adverse events sent by the study coordinator and evaluate the patient as necessary to determine whether corrective action is needed.

Further data safety and monitoring will be provided by the PI. There mechanisms for monitoring and reporting of adverse events include 1) ongoing participant contact via study personnel, and 2) weekly meetings between the PIs and study personnel. Participants are followed regularly by the study coordinator and/or one of the study therapists who is familiar with both psychiatric symptomatology and the side effects of smoking cessation pharmacotherapy. Careful attention will be paid to any increase in symptoms or new symptoms, especially in the context of use of bupropion or varenicline.

The PI will meet at least weekly with study personnel to discuss participants' reactions to the intervention, proper delivery of the intervention, and any adverse events or unanticipated problems. Frequent meetings between the investigators and the project manager will allow for ongoing progress reports, including the number of participants currently involved in the study groups, attrition rates, and scheduled data collection from participants, as well as notification and review of any AEs. Safety monitoring for adverse events (AEs) will be conducted in real time by the PI and/or project manager. The following information about adverse events will be collected: 1) the onset and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of

the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to physician, start or increase concomitant medication). Careful attention will be paid to AEs that occur with bupropion or varenicline use, and the study team will record all AEs so that any trends in AEs can be examined periodically. The PI will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution. Any adverse events will be reported to the IRB in accordance with the Duke University Medical Center IRB guidelines.

C.15. Data Analyses

Descriptive statistics will be used to summarize all study variables. For continuous variables, means, standard deviations, percentiles, ranges, box plots and histograms will be generated. For categorical variables, frequencies and proportions will be generated. Individual and mean trajectory plots of the longitudinal outcome variables will be constructed to understand their general trends over time (i.e., post-treatment, 3 months and 6 months). In addition, we will explore the variability and correlation structure of longitudinal variables. We will examine all variables to determine if parametric distributional assumptions (e.g. normality for the continuous variables) are valid. Variables not meeting distributional assumptions will either be transformed or modeled using nonparametric or semi-parametric methods (e.g. quasi-likelihood methods; McCallagh & Nelder, 1989). These descriptive variables will include smoking history and current use; level of nicotine dependence; self-efficacy, readiness to change and social support; positive and negative symptoms of schizophrenia; and depressive symptoms. In order to describe the compliance/completion of the sample in terms of smoking cessation aids and intervention completion, these variables will be summarized. In terms of descriptors for outcome measures, we will record the number of quit attempts, and utilize the time-line follow back data to identify when participants may have lapsed.

C.15.1. Missing Data. Because the main predictors of interest, treatment group and demographics, are collected at baseline, we do not anticipate much missing data. We do, however, anticipate missing values in the longitudinal outcomes owing to dropout, an inability to reach the patient, or item non-response. Mixed modeling procedures employing maximum likelihood estimates are proposed to address this issue. Mixed modeling uses all available data; as such, it can accommodate data missing at random. Because individuals with the least missing data have the most influence on model results, analyses will be conducted to determine whether missingness is systematic (i.e., associated with individual differences in either baseline parameters or time-related changes in observed variables). If data are deemed to be not missing at random, additional approaches to deal with missingness in the response will also be explored including imputing missing values by multiple imputation procedures as described by Schafer (1997). An additional analysis of smoking outcomes at end of treatment will be based on intention to treat principles, in accordance with the field standards for RCTs (Hollis & Campbell, 1999). This will use a missing=smoking approach (treating those who dropped out of the program as current smokers).

***C.15.2. Analysis Plan for AIM 1*.** Aim 1 is to refine the components of iCOMMIT. Content analysis of the cohort interviews as described above in section C.8.1 (a copy of interview question are included in Appendix B) will yield descriptive data regarding participants' perceptions of specific components of the treatment at each development phase. Participant feedback will be used to evaluate the user experience so that the phone app and counseling procedures can be enjoyable to the target population. Though the perspective of each participant in the first cohort will be strongly considered, negative feedback about an aspect of the intervention from one participant will be weighed against the feedback from others and the theoretical underpinnings of the treatment before the research team makes changes to the treatment. For example, if any participants note difficulty comprehending a treatment component or message, that component will be modified for clarity, as that does not conflict with the theoretical approach. Alternative solutions could include better therapist training, more emphasis in the treatment manual on adopting a supportive attitude toward the participant, and including more treatment aimed at soliciting social support. We will also meet weekly with the phone counselor to discuss narrative summaries of cases and the strengths and weaknesses of the treatment, as well as ease of manual use**.**

C.15.3. Analysis Plan for AIM 2. The feasibility and acceptability of iCOMMIT will be assessed *via* descriptive analyses of the ordinal-level outcomes on both the satisfaction surveys completed weekly by participants and the therapist ratings of feasibility and acceptance during both Stage 1 and 2 of the project. Participants' and therapists' responses to open-ended questions will be compiled for content analysis. In addition to evaluating participant satisfaction, we will describe

use of mCM application (adherence with mCM videos, comfort with app), medication adherence, participant smoking cessation content knowledge before and after treatment, and treatment fidelity. All of these data will provide critical information prior to planning a larger RCT.

***C.15.4. Analysis Plan for AIM 3*.** We will describe patient recruitment (proportion of patients screened/enrolled), patient treatment retention (number of sessions completed, drop outs). The proportion of patients who withdraw immediately after randomization procedures will be used to assess the feasibility of randomization. We will additionally describe the proportion of patients that quit in each arm. Logistic mixed modeling will be conducted to quantify treatment effects on smoking abstinence at post-treatment, 3 months, and 6 months. Mixed modeling is frequently used to analyze between-person differences in within-person changes. Unlike repeated-measures ANOVA, mixed models can accommodate unbalanced variances and missing data (Searle, Casella, & McCulloch, 2009). Smoking status (abstinence vs. non-abstinence) will be modeled as a function of treatment condition, a categorical time variable, and their interaction to determine whether changes in abstinence trajectories are significantly associated with treatment. An additional two-proportions z-test will be conducted on abstinence rates across the two conditions at post-treatment using ITT to generate an estimate of the effect size of iCOMMIT.

C.15.5 Analysis Plan for Aim 4. Recognizing the limitations of using this small sample in a two-group study, it is challenging to evaluate mediators and moderators of treatment. We will use Kraemer et al.'s (2002) recommended methods to identify mediators and moderators. This approach will generate hypotheses to be examined in a larger RCT, if warranted. We will explore demographic variables, nicotine-dependence, self-efficacy, delay discounting, treatment completion, medication adherence, positive and negative symptoms of schizophrenia, depressive symptoms, and neurocognitive status. Mediation and moderation analyses will be performed using mixed modeling, which can accommodate both time-varying and time-invariant predictors. Due to small sample size these will be examined individually without multiple comparison corrections. Although use of this approach could generate false positives, these are exploratory hypotheses to be examined more closely in subsequent projects.

C.16. Power and Sample Size

Power calculations provided below were performed with Power Analysis and Sample Size software (PASS, Version 12: NCSS LLC, Kaysville, Utah) and correspond to the hypothesis underlying Aim 3; that the iCOMMIT intervention will result in higher overall quit rates from cigarettes than the control. As described above, this hypothesis will be tested *via* logistic mixed modeling for which the sample size can be conservatively approximated using a Z-test for the difference of two proportions. Expected effect sizes were based on quit rates observed in our pilot work with psychiatric smokers.[15] The proposed sample of 36 participants in the RCT (18 in each treatment condition) has 79% power to detect *via* a single-tailed two-proportions *z*-test a significant treatment effect identical to what we observed amongst individuals with PTSD at post-treatment (Hertzberg et al., 2013).

References

Addington, D., Addington, J., Maticka-Tyndale, E. & Joyce, J. (1992). Reliability and validity of a depression rating scale for schizophrenics. *Schizophrenia Research,* 6, 201-08.

Alterman, A.I., Gariti, P., Cook, T.G. & Cnaan, A. (1999). Nicodermal patch adherence and its correlates. *Drug & Alcohol Dependence,* 53, 159-65.

Andreasen, N.C. (1982). Negative symptoms in schizophrenia. Definition and reliability. *Archives of General Psychiatry,* 39, 784-8.

Andreasen, N.C., Arndt, S., Miller, D., Flaum, M. & Nopoulos, P. (1995). Correlational studies of the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Postivie Symptoms: An overview and update. *Psychopathology,* 28, 7-17.

Anthenelli, R.M., Benowitz, N.L., West, R., St Aubin, L., McRae, T., Lawrence, D., Ascher, J., Russ, C., Krishen, A., Evins, A.E. (2016) Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomised, placebo-controlled clinical trial. Epub ahead of print, http://dx.doi.org/10.1016/S0140-6736(16)30272-0.

Baer, J.S., Holt, C.S. & Lichtenstein, E. (1986). Self-efficacy and smoking reexamined: Construct validity and clinical utility. *Journal of Consulting and Clinical Psychology,* 54, 846-52.

Balmford, J., Borland, R., Hammond, D. & Cummings, K.M. (2011). Adherence to and reasons for premature discontinuation from stop-smoking medications: Data from the ITC Four-Country Survey. *Nicotine & Tobacco Research,* 13, 94-102. PMCID: PMC3028191.

Bastian, L.A., Fish, L.J., Gierisch, J.M., Rohrer, L.D., Stechuchak, K.M. & Grambow, S.C. (2012). Comparative effectiveness trial of family supported smoking cessation intervention versus standard telephone counseling for chronically ill veterans using proactive recruitment. *Comparative Effectiveness Research,* 2, 45-56.

Bradley, K. A., & Bush, K. R. (1998). Screening for problem drinking: comparison of CAGE and AUDIT. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Journal of General Internal Medicine, 13*(6), 379-388.

Carpenter, V.L., Hertzberg, J.S., Kirby, A.C., Calhoun, P.S., Moore, S.D., Dennis, M.F., Dennis, P.A., Dedert, E.A., Hair, L.P. & Beckham, J.C. (2014). Multi-component smoking cessation treatment including mobile contingency management for smoking cessation in homeless veteran smokers. *Manuscript submitted for publication*.

Carroll, K.M. (2000). A general system for evaluating therapist adherence and competence in psychotherapy research in the addictions. *Drug and Alcohol Dependence,* 57, 225-38.

Catz, S.L., Jack, L.M., McClure, J.B., Jarvitz, H.S., Deprey, M., Zbikowski, S.M., McAfee, T., Richards, J. & Swan, G.E. (2011). Adherence to varenicline in the COMPASS smoking cessation intervention trial. *Nicotine & Tobacco Research,* 13, 361-8. PMCID: PMC3082504.

Centers for Disease Control and Prevention. (2004). Cigarette smoking among adults-United States, 2002. *Morbidity and Mortality Weekly Report,* 53, 427-31.

Centers for Disease Control and Prevention. (2008). Smoking-attributable mortality, years of potential life lost, and productivity losses - United States, 2000-2004. *Morbidity and Mortality Weekly Report,* 57, 1226-8.

Cerimele, J. & Durango, A. (2012). Does varenicline worsen psychiatric symptoms in patients with schizophrenia or schizoaffective disorder? A review of published studies. *Journal of Clinical Psychiatry, 73*, e1039-e1047.

Chambers, R.A., Krystal, J.H. & Self, D.W. (2001). A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biological Psychiatry,* 50, 71-83. PMCID: PMC2913410.

Cooper, T.V., DeBon, M.W., Stockton, M., Klesges, R.C., Steenbergh, T.A., Sherrill-Mittleman, D., Jennings, L.C. & Johnson, K.C. (2004). Correlates of adherence with transdermal nicotine. *Addictive Behaviors,* 29, 1565-78.

Copeland, A. L., Brandon, T. H., & Quinn, E. P. (1995). The Smoking Consequences Questionnaire-Adult: Measurement of smoking outcome expectancies of experienced smokers. *Psychological Assessment, 7*(4), 484-494.

Curry, S., Wagner, E.H., & Grothaus, L.C. (1990). Intrinsic and extrinsic motivation for smoking cessation. *Journal of Consulting and Clinical Psychology, 58*(3), 310-316.

de Leon, J. & Diaz, F.J. (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Research,* 76, 1351-57.

Dickerson, F., Origoni, A., Schroeder, J., Schweinfurth, L. A., Stallings, C., Savage, C. L., ... & Yolken, R. (2016). Mortality in schizophrenia and bipolar disorder: Clinical and serological predictors. *Schizophrenia Research, 170*(1), 177-183.

Elman, I., Ariely, D., Mazar, N., Aharon, I., Lasko, N.B., Macklin, M.L., Orr, S.P., Lukas, S.E. & Pitman, R.K. (2005). Probing reward function in post-traumatic stress disorder with beautiful facial images. *Psychiatry Research,* 135, 179-83.

Epstein, E.E., McCrady, B.S., Morgan, T.J., Cook, S.M., Kugler, G. & Ziedonis, D. (2007). The successive cohort design: A model for developing new behavioral therapies for drug use disorders, and the application to behavioral couple treatment. *Addictive Disorders and Their Treatment,* 6, 1-19.

Evins, A.E. (2008). Varenicline treatment for smokers with schizophrenia: A case series. *Journal of Clinical Psychiatry, 69*, 1016.

Fiore, M.C., Bailey, W.C., Cohen, S.J., Dorfman, S.F., Goldstein, M.G. & Gritz, E.R. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: U.S. Department of Health and Human Services; 2000.

Fiore, M.C., Jaen, C.R., Baker, T.B., Bailey, W.C., Benowitz, N., Curry, S.J., Dorfman, S.F., Froelicher, E.S., Goldstein, M.G., Healton, C.G., Henderson, P.N., Heyman, R.B., Koh, H.K., Kottke, T.E., Lando, H.A., Mecklenburg, R.E., Mermelstein, R.J., Mullen, P.D., Orleans, C.T., Robinson, L., Stitzer, M.L., Tommasello, A.C., Villejo, L. & Wewers, M.E. (2008). Treating tobacco use and dependence: 2008 update.

First, M.B., Spitzer, R.L., Gibbon, M. & Williams, J.B.W. *Structured Clinical Interview for the DSM-IV Axis I Disorders*. New York, NY: Biometrics Research , New York State Psychiatric Institute; 1996.

Freitas, S., Simões, M.R., Marôco, J., Alves, L. & Santana, I. (2012). Construct validity of the Montreal Cognitive Assessment (MoCA). *Journal of International Neuropsychological Sociology,* 18, 242-50.

Gallagher, S.M., Penn, P.E., Schindler, E. & Layne, W. (2007). A comparison of smoking cessation treatments for persons with schizophrenia and other serious mental illnesses. *Journal of Psychoactive Drugs,* 39, 487-97.

Garcia-Rodriguez, O., Secades-Villa, R., Weidberg, S. & Yoon, J.H. (2013). A systematic assessment of delay discounting in relation to cocaine and nicotine dependence. *Behav Processes,* 99, 100-5.

George, T.P., Ziedonis, D.M., Feingold, A., Pepper, W.T., Satterburg, C.a., Winkel, J., Rounsaville, B.J. & Kosten, T.R. (2000). Nicotine and transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *American Journal of Psychiatry,* 157, 1835-42.

George, T.P. & Ziedonis, D.M. (2009). Addressing tobacco dependence in psychiatric practice: Promises and pitfalls. *Canadian Journal of Psychiatry,* 54, 353-55.

Glimcher, P.W. & Rustichini, A. (2004). Neuroeconomics: The consilience of brain and decision. *Science,* 306, 447-52.

Heather, N., Rollnick, S. & Bell, A. (1993). Predictive validity of the Readiness to Change Questionnaire. *Addiction,* 88, 1667-77.

Heatherton, T.F., Kozlowski, L.T., Frecker, R.C. & Fagerström, K.O. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction,* 86, 1119-27.

Hertzberg, J.S., Carpenter, V.L., Kirby, A.C., Calhoun, P.S., Moore, S.D., Dennis, M.F., Dennis, P.A., Dedert, E.A. & Beckham, J.C. (2013). Mobile contingency management as an adjunctive smoking cessation treatment for smokers with posttraumatic stress disorder. *Nicotine & Tobacco Research,* 15, 1934-38. PMCID: PMC3790624.

Hollands, G.J., Sutton, S., McDermott, M.S., Marteau, T.M. & Aveyard, P. (2013). Adherence to and consumption of nicotine replacement therapy and the relationship with abstinence within a smoking cessation trial in primary care. *Nicotine & Tobacco Research,* 15, 1537-44. PMCID: PMC3741059.

Hollis, S. & Campbell, F. (1999). What is meant by intention to treat analysis? Survey of published randomised controlled trials. *British Medical Journal,* 319, 670-4. PMCID: PMC28218.

Hopper, J.W., Pitman, R.K., Su, Z., Heyman, G.M., Lasko, N.B., Macklin, M.L., Orr, S.P., Lukas, S.E. & Elman, I. (2008). Probing reward function in posttraumatic stress disorder: Expectancy and satisfaction with monetary gains and losses. *Journal of Psychiatric Research,* 42, 802-7. PMCID: PMC2551554.

Horvath, T., Azman, H., Kennedy, G.E. & Rutherford, G.W. (2012). Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection (Review). *Cochrane Database of Systematic Reviews,* 3, CD009756.

Howes, O.D. & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III--the final common pathway. *Schizophrenia Bulletin,* 35, 549-62. PMCID: PMC2669582.

Hughes, J., Keely, J., Niaura, R., Ossip-Klein, D., Richmond, R. & Swan, G. (2003). Measures of abstinence in clinical trials: Issues and recommendations. *Nicotine & Tobacco Research,* 5, 13-25.

Keltner, N.L. & Grant, J.S. (2006). Smoke, smoke, smoke that cigarette. *Psychiatric Care,* 42, 256-61.

Kraemer, H.C., Wilson, G.T., Fairburn, C.G. & Agras, W.S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry,* 59, 877-83.

Kring, A.M., Gur, R.E., Blanchard, J.J., Horan, W.P., & Reise, S.P. (2013). The Clinical Assessment Interview for Negative Symptoms (CAINS): Final development and validation. *American Journal of Psychiatry, 170*, 165-172.

Krishnan-Sarin, S., Duhig, A.M., McKee, S.A., McMahon, T.J., Liss, T., McFetridge, A. & Cavallo, D.A. (2006). Contingency management for smoking cessation in adolescent smokers. *Experimental Clinical Psychopharmacology,* 14, 306-10.

Lamb, R., Morral, A., Kirby, K., Iguchi, M. & Galbicka, G. (2004). Shaping smoking cessation using percentile schedules. *Drug & Alcohol Dependence,* 76, 247-59.

Lamb, R., Morral, A., Kirby, K., Javors, M., Galbicka, G. & Iguchi, M. (2007). Contingencies for change in complacent smokers. *Experimental Clinical Psychopharmacology,* 15, 245-55.

Lasser, K., Boyd, J.W., Woolhander, S., Himmelstein, D.U., McCormick, D. & Bor, D.H. (2000). Smoking and mental illness: A population-based prevalence study. *Journal of the American Medical Association,* 284, 2606-10.

Lewis-Esquerre, J.M., Colby, S.M., Tevyaw, T.O., Eaton, C.A., Kahler, C.W. & Monti, P.M. (2005). Validation of the timeline follow-back in the assessment of adolescent smoking. *Drug and Alcohol Dependence,* 79, 33-43.

McClave, A.K., McKnight-Eily, L.R., Davis, S.P. & Dube, S.R. (2010). Smoking characteristics of adults with selected lifetime mental illnesses: Research from the 2007 National Health Interview Survey. *American Journal of Public Health,* 196, 116-21. PMCID: PMC2978196.

McCullagh, P. & Nelder, J.A. *Generalized Linear Models*. 2nd ed. London: Chapman & Hall; 1989.

McFall, M., Saxon, A., Malte, C., Chow, B., Bailey, S., Baker, D., Beckham, J., Boardman, K.D., Carmody, T.P., Joseph, A., Smith, M.W., Shih, M., Lu, J., Holodniy, M. & Lavori, P.W. (2010). Integrating tobacco cessation into mental health care for posttraumatic stress disorder: A randomized controlled trial. *Journal of the American Medical Association,* 304, 2485-93.

Mokdad, A.H., Marks, J.S., Stroup, D.F. & Gerberding, J.L. (2004). Actual causes of death in the United States. *Journal of the American Medical Association, 291*, 1238-45.

Morisky, D.E., Green, L.W. & Levine, D.M. (1986). Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care,* 24, 67-74.

National Institute on Drug Abuse. *NIH Guide: Behavioral Therapies Development Program*. Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services; 2003.

Neria, Y., Bromet, E.J., Sievers, S., Lavelle, J., Fochtmann, J.L. (2002). Trauma exposure and posttraumatic stress disorder in psychosis: Findings from a first-admission cohort. *Journal of Consulting and Clinical Psychology, 70*, 246 –251.

Petry, N.M. (2001). Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. *Psychopharmacology (Berl),* 154, 243-50.

Petry, N.M. (2010). Contingency management treatments: Controversies and challenges. *Addiction,* 105, 1507-09.

Pop-Eleches, C., Thirumurthy, H., Habyarimana, J.P., Zivin, J.G., Goldstein, M.P., de Walque, D., MacKeen, L., Haberer, J., Kimaiyo, S., Sidle, J., Ngare, D. & Bangsberg, D.R. (2011). Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: A randomized controlled trial of text message reminders. *AIDS,* 25, 825-34. PMCID: PMC3718389.

Potenza, M.N., Sofuoglu, M., Carroll, K.M. & Rounsaville, B.J. (2011). Neuroscience of behavioral and pharmacological treatments for addictions. *Neuron,* 69, 695-712. PMCID: PMC3063555.

Prevention and Management of Disruptive Behavior, VHA Central Office (2013). *Prevention and Management of Disruptive Behavior: Supplement for Community Based Workers.* Washington, DC: VHA Central Office.

Rausch, F., Mier, D., Eifler, S., Esslinger, C., Schilling, C., Schirmbeck, F., Englisch, S., Meyer-Lindenberg, A., Kirsch, P. & Zink, M. (2014). Reduced activation in ventral striatum and ventral tegmental area during probabilistic decision-making in schizophrenia. *Schizophrenia Research,* 156, 143-9.

Rollnick, S., Heather, N., Gold, R. & Hall, W. (1992). Development of a short "Readiness to Change" questionnaire for use in brief opportunistic interventions. *British Journal of Addiction,* 87, 743-54.

Romanowich, P., Mintz, J. & Lamb, R.J. (2009). The relationship between self-efficacy and reductions in smoking in a contingency management procedure. *Experimental Clinical Psychopharmacology,* 17, 139-45. PMCID: PMC3105444.

Rounsaville, B.J., Carroll, K.M. & Onken, L.S. (2001). A stage model of behavioral therapies research: Getting started and moving on from Stage 1. *Clinical Psychology: Science and Practice,* 8, 133-42.

Russell, M.A.H., Peto, J., & Patel, U.A. (1974). The classification of smoking by factorial structure of motives. *Journal of the Royal Statistical Society. Series A (General)*, 313-346.

Saha, S., Chant, D. & McGrath, J. (2007). A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry,* 64, 1123-31.

Sailer, U., Robinson, S., Fischmeister, F.P., Konig, D., Oppenauer, C., Lueger-Schuster, B., Moser, E., Kryspin-Exner, I. & Bauer, H. (2008). Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. *Neuropsychologia,* 46, 2836-44.

Schafer, J.L. *Analysis of Incomplete Multivariate Data*. Boca Raton, FL: Chapman & Hall/CRC; 1997.

Schultz, W. (2006). Behavioral theories and the neurophysiology of reward. *Annual Review of Psychology,* 57, 87-115.

Searle, S.R., Casella, G. & McCulloch, C.E. *Variance components*. New York: Wiley; 2009.

Selby, P., Voci, S.C., Zawertailo, L.A., George, T.P. & Brands, B. (2010). Individualized smoking cessation treatment in an outpatient setting: Predictors of outcome in a sample with psychiatric and addictions co-morbidity. *Addictive Behaviors,* 35, 811-17.

Shiffman, S., Balabanis, M.H., Paty, J.A., Engberg, J., Gwaltney, C.J. & Liu, K. (2000). Dynamic effects of self-efficacy on smoking lapse and relapse. *Health Psychology,* 19, 315-23.

Shiffman, S., Sweeney, C.T., Ferguson, S.G., Sembower, M.A. & Gitchell, J.G. (2008). Relationship between adherence to daily nicotine patch use and treatment efficacy: Secondary analysis of a 10-week randomized, double-blind, placebo-controlled clinical trial simulating over-the-counter use in adult smokers. *Clinical Therapeutics,* 30, 1852-58.

Sirota, A.D., Rohsenow, D.J., MacKinnon, S.V., Martin, R.A., Eaton, C.A., Kaplan, G.B., Tidey, J.W., & Swift, R.M. (2010). Intolerance for Smoking Abstinence Questionnaire: Psychometric properties and relationship to tobacco dependence and abstinence. *Addictive Behavior, 35*, 686-693.

Skinner, H.A. (1982). The Drug Abuse Screening Test. *Addictive Behaviors, 7*, 363-371.

Stapleton, J.A., Watson, L., Spirling, L.I., Smith, R., Milbrandt, A., Ratcliffe, M., Sutherland, G. (2008). Varenicline in the routine treatment of tobacco dependence: a pre–post comparison with nicotine replacement therapy and an evaluation in those with mental illness. *Addiction, 103*, 146-154.

Tidey, J.W., Rohsenow, D.J., Kaplan, G.B., Swift, R.M. & Reid, N. (2011). Effects of contingency management and bupropion on cigarette smoking in smokers with schizophrenia. *Psychopharmacology (Berl),* 217, 279-87. PMCID: PMC3685403.

Toll, B.A., McKee, S.A., Martin, D.J., Jatlow, P. & O'Malley, S.S. (2007). Factor structure and validity of the Medication Adherence Questionnaire (MAQ) with cigarette smokers trying to quit. *Nicotine & Tobacco Research,* 9, 597-605.

Tsoi, D.T., Porwal, M. & Webster, A.C. (2010). Efficacy and safety of bupropion for smoking cessation and reduction in schizophrenia: Systematic review and meta-analysis. *British Journal of Psychiatry,* 196, 346-53.

Tsoi, D.T., Porwal, M. & Webster, A.C. (2013). Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database of Systematic Reviews,* 2, CD007253.

Tuldra, A., Ferrer, M.J., Fumaz, C.R., Bayés, R., Paredes, R., Burger, D.M. & Clotet, B. (1999). Monitoring adherence to HIV therapy. *Archives of Internal Medicine,* 159, 1376-77.

Weathers, F.W., Litz, B.T., Keane, T.M., et al. (2013). The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD at www.ptsd.va.gov.

Weiner, E., Buchholtz, A., Coffay, A., Liu, F., McMahon, R.P., Buchanan, R.W., & Kelly, D.L. (2011). Varenicline for smoking cessation in people with schizophrenia: A double blind randomized pilot study. *Schizophrenia Research, 129*, 94-95.

Williams, J.M., Anthenelli, R.M., Morris, C.D., Treadow, J., Thompson, J.R., Yunis, C., George, T.P. (2012). A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *Journal of Clinical Psychiatry, 73*, 654-660.

Williams, R.B., Barefoot, J.C., Califf, R.M., Haney, T.L., Saunders, W.B., Pryor, D.B., Hlatky, M.A., Siegler, I.C. & Mark, D.B. (1992). Prognostic importance of social and economic resources among medically treated patients with angiographically documented coronary artery disease. *Journal of the American Medical Association,* 267, 520-4.

Ziedonis, D., Hitsman, B., Beckham, J.C., Zvolensky, M., Adler, L.E., Audrain-McGovern, J., Breslau, N., Brown, R.A., George, T.P., Williams, J., Calhoun, P.S. & Riley, W.T. (2008). Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine & Tobacco Research,* 10, 1691-715.

Zhang, Y. & Wildermuth, B.M. Applications of social research methods to questions in information and library science. In: Wildemuth, B., ed. *Qualitative analysis of content*. Westport, CT: Libraries Unlimited; 2009b:308-19.

Zhang, Y. & Wildermuth, B.M. Qualitative analysis of content. In: Wildemuth, B., ed. *Applications of social research methods to questions in information and library science*. Westport, CT: Libraries Unlimited; 2009a:308-19.