PROTOCOL TITLE:

Enhancing Smoking Cessation in the Homeless Population

ClinicalTrials.gov:

NCT01932996

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VERSION NUMBER/DATE:

Version 1, November 15, 2017

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

Table of Contents

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ABBREVIATIONS/DEFINITIONS

Include any abbreviations or definitions for key or technical terms you use in your protocol.

- [Abbreviation/Definition 1]
- [Abbreviation/Definition 2]
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All abbreviations used in this document are first spelled out when used for the first time with the abbreviated acronym in parenthesis.

STUDY SUMMARY

Study Title	Enhancing Smoking Cessation in the Homeless Population
Study Design	The goal of this study is to enhance smoking cessation rates for homeless smokers by testing effects of 1) an Intensive Smoking Intervention, and 2) integrating alcohol abuse treatment with smoking cessation. We initially utilized a 3-group randomized design to test study hypotheses. The three study conditions were: 1) Integrated Intensive Smoking plus Alcohol intervention using cognitive behavioral therapy, CBT—(IS+A); 2) Intensive Smoking Intervention using CBT—(IS); or 3) Usual Care (brief smoking cessation and brief alcohol counseling both based on the USPHS's Guidelines)—(UC). The addition of the alcohol use criteria resulted in nearly two-thirds of those screened to be deemed ineligible. Consequently the study was revised to eliminate the Intensive Smoking Intervention using CBT—(IS) arm and the study period reduced from 52 weeks to 26 weeks to improve enrollment into the intensive smoking and alcohol and usual care arms. All participants receive 12-week of treatment with the nicotine patch plus nicotine gum/lozenge. Counseling follows the protocol used in a recent study of alcohol dependent smokers and includes weekly individual sessions for 3 months. Both study conditions will have equal number of study contacts. Study staff make retention contacts with participants in the community during weeks that do not have study visits scheduled. Primary smoking outcome is cotinine-verified 7-day smoking abstinence at week 26 follow-up while secondary outcome is prolonged smoking abstinence at weeks 12 and 26. Secondary alcohol outcome will be self-reported continuous alcohol abstinence for 90 days at week 26. Recruitment and retention will be enhanced by use of gift cards, bus passes, and other non-monetary incentives. Participants will be enrolled from homeless shelters and facilities in the 7-county greater Minneapolis/St. Paul metro area.
Primary Objective	**Hypothesis 1:** At 26 weeks post randomization, homeless smokers who receive Integrated Smoking

	plus Alcohol Intervention (IS+A) will have significantly better biochemically-verified 7-day abstinence rate from cigarette smoking compared to those who received Usual Care (UC). **Hypothesis 2:** At 26 weeks post randomization, homeless smokers who receive Integrated Smoking plus Alcohol intervention (IS+A) will have significantly better 90-day abstinence rate from alcohol consumption compared to smokers who receive Usual Care (UC). **Exploratory Aim** **Hypothesis 3:** At 26 weeks post randomization, homeless smokers who receive Intensive Smoking Intervention (IS) will have significantly higher biochemically-verified 7-day abstinence rate from cigarette smoking compared to those who receive Usual Care (UC).
Secondary Objective(s)	1. To evaluate how smoking cessation or reduction relate to psychosocial factors such as levels of depression, hopelessness, and perceived stress at weeks 12 and 26 follow-up 2. To evaluate how alcohol abstinence or reduction relate to psychosocial factors such as levels of depression, hopelessness, and perceived stress at 12 and 26 weeks follow-up. 3. To evaluate how treatment outcomes relate to history of other substance abuse 4. To evaluate, how treatment outcomes relate to opportunities for employment and housing, as well as overall health and well-being. 5. To evaluate participants' perceptions of the acceptability and usefulness of components of the various interventions
Research Intervention(s)/Investigational Agents	NA
IND/IDE # (if applicable)	NA
Investigational Drug Services # (if applicable)	NA
Study Population	Homeless adult men and women who smoke cigarettes and drink alcohol
Sample Size (number of participants)	428
Study Duration for Individual Participants	26 weeks

1.0 Objectives

1.1 Purpose:

Although the overall prevalence of smoking in the United Sates has declined, rates remain strikingly high (70%) in homeless populations. A majority of homeless smokers also abuse alcohol and other drugs which makes quitting more difficult and heightens the health consequences of tobacco use. However, most smoking cessation research has excluded this most vulnerable segment of our population. Over the past several years, our research team conducted studies aimed at reducing tobacco use in homeless populations. The first National Institute of Health (NIH)-funded (R01HL081522; Okuyemi, Pl) smoking cessation clinical trial (n=430) targeted homeless smokers with 8-week treatment with nicotine patch and 6 sessions of motivational interviewing (Ml). This relatively low intensity study showed cotinine-verified 7-day quit rates of 9.3% for Ml vs. 5.6% for Brief Advice at 26 weeks. We also found that quitting smoking was associated with reduced alcohol use. These smoking quit rates are low compared to the general population, demonstrating the challenge for tobacco interventions in this population and the need for more research. The goal of this study is to evaluate interventions designed to enhance smoking cessation rates for homeless smokers by testing the effects of 1) intensive smoking intervention (i.e. higher dose and duration than our previous R01), and 2) integrating alcohol abuse treatment with smoking cessation. We utilize a 2-group randomized design to test study hypotheses. The study conditions are: 1) Integrated Intensive Smoking intervention using cognitive behavioral therapy (CBT) plus Alcohol intervention -(IS+A) and, 2) Usual Care (brief smoking cessation and brief alcohol counseling both based on the US Public Health Service's Guidelines). In addition, all participants receive 12-weeks of treatment with a combination of nicotine patch plus gum or lozenge.

2.0 Background

2.1 Significance of Research Question/Purpose:

Despite strikingly high rates of tobacco use in homeless populations, there is limited empirical data about how to help homeless smokers quit smoking. Because quit rates are low in homeless populations it is critical to develop more powerful interventions for improving cessation rates. Given that the majority of homeless smokers also abuse alcohol, a logical next step to improve smoking cessation rates in this group is to address their alcohol abuse along with a more intensive pharmacological and behavioral smoking cessation intervention.

2.2 Preliminary Data:

2.3 This study is a follow-up study to the initial study, Power to Quit (PTQ) that used a similar study design. An association was noted between smoking cessation/reduction and alcohol cessation/reduction. We conducted a secondary analysis to examine the association between smoking cessation and substance abuse in the PTQ study. Participants with verified abstinence at week 26 had greater reduction in alcohol drinking days compared to participants who did not quit smoking (-3.8 vs. -0.8; p=0.05). We also examined the quit rates at 26 weeks by alcohol use status at 8 weeks among the subset that reported drinking alcohol on one or more days at baseline enrollment. Alcohol drinkers at baseline who reported quitting alcohol at 8 weeks follow-up had higher smoking abstinence rate (10.1%) at week 26 follow-up compared with those remained drinkers.

2.4 Existing Literature:

1) Goldade K, Whembolua GL, Thomas J, et al. Designing a smoking cessation intervention for the unique needs of homeless persons: a community-based randomized clinical trial. Clinical Trials. 2011 Dec;8(6):744-54. This paper describes the design of the study, recruitment procedures, eligibility criteria, and detailed overview of the intervention components. These proven and effective recruitment and retention methods will be used in the proposed study;

2) Okuyemi KS, Goldade K, Whembolua GL, Thomas JL, Eischen S, Guo H, Connett JE, Grant J, Ahluwalia JS, Resnicow K, Owen G, Gelberg L, Jarlais DD. Smoking characteristics and comorbidities in the power to quit randomized clinical trial for homeless smokers. Nicotine Tob Res.2013 Jan;

15(1):22-8.. This paper describes the smoking characteristics and co-morbid conditions of study participants including the prevalence of alcohol use and abuse among homeless smokers;

3) Okuyemi KS, Goldade K, Whembolua GL, et al. Effects of Motivational Interviewing and Nicotine Patch for Smoking Cessation among Homeless Smokers. (In press): Addiction. Using intent-to-treat procedures counting those lost to follow-up as smokers, quit rates at week 26 were 9.3% and 5.6% for intervention and control respectively (p=0.15). Those adherent to MI (attended 5 of 6 sessions) had higher quit rates than nonadherents at week 8 (10.9% vs. 3.0%; p=0.02) and week 26 (8.5% vs. 4.0%; p=0.19). We used a GEE logistic regression (Figure 1), model to analyze the longitudinal outcomes for the CO-verified abstinence at weeks 1, 2, 4, 6, 8 and 26 including time and intervention group as predictors. The odds ratio for the MI vs. Control was 1.40 (95% CI=0.93-2.11; p= 0.11);

4) Borja C, Goldade K, Olayinka A, et al. Participation of Homeless Persons in a Smoking Cessation Randomized Controlled Trial. (Submitted)

Addictive Behaviors. This paper described the recruitment and eligibility of homeless smokers who participated in the PTQ study. Working with local shelters, a total of 847 adult smokers were screened for study eligibility of which 580 (68.5%) met eligibility criteria. Of those eligible, 430 (74.1%) returned for randomization. Eligible participants who returned for randomization were older and more likely to have a phone number compared to eligible participants who were not enrolled in the study. Knowledge of these factors including inclusion and exclusion criteria may help researchers tailor criteria that accurately identify and include homeless smokers in future clinical trials.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Primary Aims
To assess the efficacy of a) intensive smoking intervention and b) integrating alcohol abuse treatment with smoking cessation among homeless smokers.

Primary Hypotheses
Hypothesis 1: At 26 weeks post randomization, homeless smokers who receive Integrated Smoking plus Alcohol Intervention (IS+A) will have significantly better biochemically-verified 7-day abstinence rate from cigarette smoking compared to those who received Usual Care (UC).

Hypothesis 2: At 26 weeks post randomization, homeless smokers who receive Integrated Smoking plus Alcohol intervention (IS+A) will have significantly better 90-day abstinence rate from alcohol consumption compared to smokers who receive Usual Care (UC).

Exploratory Aim
Hypothesis 3: At 26 weeks post randomization, homeless smokers who receive Intensive Smoking Intervention (IS) will have significantly higher biochemically-verified 7-day abstinence rate from cigarette smoking compared to those who receive Usual Care (UC).

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

1. To evaluate how smoking cessation or reduction relate to psychosocial factors such as levels of depression, hopelessness, and perceived stress at weeks 12 and 26 follow-up.
2. To evaluate how alcohol abstinence or reduction relate to psychosocial factors such as levels of depression, hopelessness, and perceived stress at 12 and 26 weeks follow-up.
3. To evaluate how treatment outcomes relate to history of other substance abuse.

4. To evaluate, how treatment outcomes relate to opportunities for employment and housing, as well as overall health and well-being.
5. To evaluate participants' perceptions of the acceptability and usefulness of components of the various interventions.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

The study is a 2-group randomized design to test study hypotheses. The two study conditions are 1) Integrated Intensive Smoking plus Alcohol intervention using cognitive behavioral therapy, CBT—(IS+A); 2) Usual Care (brief smoking cessation and brief alcohol counseling both based on the USPHS's Guidelines)—(UC). All participants receive 12-weeks of treatment with a nicotine patch plus nicotine gum/lozenge. Counseling follows the protocol used in a recent study of alcohol dependent smokers and includes weekly individual sessions for 3 months. All study participants complete weekly study surveys during the first 12 weeks and at weeks 14, 16, 18, 22 and 26. Both study conditions have equal number of study contacts. Study staff make retention contacts with participants in the community during weeks that do not have study visits scheduled. Primary smoking outcome is cotinine-verified 7-day smoking abstinence at week 26 follow-up while secondary outcome is prolonged smoking abstinence at weeks 12 and 26. Secondary alcohol outcome is self-reported continuous alcohol abstinence for 90 days at week 26. Recruitment and retention are enhanced by use of gift cards, bus passes, weekly raffles, and other non-monetary incentives. Participants are enrolled from homeless shelters and facilities in the 7-county greater Minneapolis/St. Paul metro area.

4.2 Drug/Device Handling:

N/A

4.3 IND/IDE:

N/A

4.4 Biosafety:
N/A

4.5 *Stem Cells:*
N/A

5.0 Procedures Involved

5.1 Study Design:

The study is testing effects of an intensive smoking intervention integrating an alcohol abuse intervention with smoking cessation using a 2-group randomized design. The two study conditions are 1) Integrated Intensive

Smoking plus Alcohol intervention using cognitive behavioral therapy, CBT—(IS+A) or 2) Usual Care (brief smoking cessation and brief alcohol counseling both based on the United States Public Health Service's Guidelines)—(UC). All participants receive 12 weeks of treatment with nicotine patches plus nicotine gum or lozenges. Participants randomized to the counseling arm receive cognitive behavioral therapy for tailored for smoking cessation and for alcohol cessation. Both study conditions have equal number of study contacts. Participants are scheduled for weekly visits during the first 12 weeks of the study and also at weeks 14, 16, 18, 22, and 26. Study staff make retention contacts with participants in the community during weeks that do not have study visits scheduled. Primary smoking outcome is cotinine-verified 7-day smoking abstinence at week 26 follow-up while secondary outcome is prolonged smoking abstinence at weeks 12 and 26. Secondary alcohol outcome is self-reported continuous alcohol abstinence for 90 days at week 26. Recruitment and retention are enhanced by use of gift cards, weekly raffles, bus passes, and other non-monetary incentives. Participants are enrolled from homeless shelters and facilities in the 7-county greater Minneapolis/St. Paul metro area.

5.2 Study Procedures:

Participants are recruited at Twin City area homeless shelters and service organizations serving homeless adults to complete an eligibility survey to determine if they meet the eligibility requirements of the study. Eligible participants are scheduled for the baseline enrollment visit at which time study staff explain the study in detail, obtain consent, administer a baseline date collection survey and randomize the participant to one of the two study arms. Participants are scheduled for weekly data collection surveys and counseling sessions for those randomized to the counseling arm for the first 12 weeks of the study and every other week (14, 16 and 18) and at weeks 22 and 26.

In the usual care, or control, arm, participants receive 12 weeks of NRT (nicotine replacement treatment) and one-time brief (~15 minutes) counseling for smoking cessation and alcohol cessation. The smoking cessation counseling is based on the 5 A's model (Ask, Advise, Assess, Assist, Arrange) recommended by the US Public Health Service Clinical Practice Guidelines. Consistent with the guidelines, counselors conduct the following procedures: a) congratulate the participant on enrolling in the study, b) describe the harms related to smoking and the benefits of quitting, c) advise the participant to quit immediately, d) assist participants to set a quit date, e) encourage participants to tell friends and families about their quitting, and f) describe potential relapse situations and other barriers to quitting. The brief alcohol counseling follows Public Health Service guidelines and include elements such as a) presenting screening results, b) identifying risks, c) discussing consequences, d) soliciting commitment, e)

identifying goals, and f) giving advice and encouragement. At the end of the session, participants interested in additional smoking or alcohol intervention are referred to local and national treatment programs.

Participants in intensive integrated smoking and alcohol counseling condition receive 12 weeks of NRT treatment plus weekly individual cessation counseling sessions. Counseling utilize CBT (cognitive behavioral therapy) techniques. The counselor assists participant to set and prepare for their quit date targeted for the day after randomization. Initial CBT sessions focus on identifying situations, activities, moods, and thoughts associated with cigarette smoking, strategies for coping with trigger events and smoking urges, etc. Counseling is also be tailored to address challenges peculiar to homeless persons including boredom, lack of structure in daily life, and dealing with the stress related to meeting competing social needs (e.g. food, housing, safety, grooming, etc.). The remaining sessions focus on relapse prevention. This protocol was used in a recent study by our research team.

The alcohol counseling is distinct from smoking counseling and does not emphasize similarities between quitting smoking and stopping alcohol and drug use. This is based on findings from a study that reported that emphasizing these similarities led to worse drinking outcomes compared to concurrent treatment that did not emphasize the similarities. Alcohol treatment is based on a CBT manual developed for Project MATCH, an 8 year NIH multi-site alcohol treatment study and was used by our research team in a recent study. About 40 minutes of each session is devoted to alcohol treatment to include identifying alcohol antecedents, coping with alcohol urges, managing thoughts about alcohol, problem solving, drink refusal skills, planning for emergencies, assertiveness training, and enhancing social support networks for alcohol abstinence.

At weekly study sessions staff ask about any issues the participant may be experiencing with the products. An adverse event form is completed if participants report any side effects from use of the nicotine replacement products. Participants receive additional two-week supplies as needed.

At each study visit, the study survey asks if the participant was hospitalized or visited the emergency room since their last visits. An adverse event form is completed if either event occurred. Study staff also assess to determine if the participant is currently exhibiting incoherence, disorganized speech, or marked loosening of associations and if so, administer the Short Blessed Test to assess cognitive concerns in the areas of orientation, memory, and concentration. Additionally, at each study visit participants are assessed for suicidal ideation. The Columbia Suicide Severity Rating Scale is administered anytime a participant answers affirmatively to the question: "over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?" If the result of the Columbia indicates they have intention or a plan, they are

escorted by study staff to the medical clinic at the shelter, to COPE (Community Outreach for Psychiatric Emergencies), or to the nearest hospital emergency room.

Participants are compensated with a Visa or American Express gift card of varying amounts at each study visits and also receive a $5 Subway gift card or a non-monetary incentive such as a backpack, word finder game, pocket calendar, playing cards, or water bottle. During the first 12 weeks and at weeks 16 and 26, participants are offered a raffle draw for an additional incentive to increase retention at these key data collection points. Visa/American Express card denominations vary from $10 for most visits to $75 at week 26 for the final study visit and data collection survey.

5.3 Follow-Up:

Data collection includes biologic (height, weight, salivary cotinine, alcohol breathalyzer, expired carbon monoxide and urine pregnancy tests for women of child-bearing age), demographic, homeless history, smoking history, NRT adherence and data from the following instruments:

Alcohol Use Disorders Identification Test (AUDIT), Cessation Progress, Treatment Self-Regulation for Smoking, Fagerstrom Test for Nicotine Dependence, Morisky Adherence, modified MN Nicotine Withdrawal Scale, Brief Questionnaire of Smoking Urges, Pittsburgh Sleep Quality Index, Clinical Withdrawal Assessment of Alcohol Scale Revised (CIWA), Columbia Suicide Severity Rating Scale, Penn Alcohol Craving Scale, Rost-Burnham substance use screener, PHQ-9, Mini-International Neuropsychiatric Interview (MINI) Anxiety, MINI Psychotic Symptoms, Short-Blessed Test, Perceived Stress Scale, Self-Efficacy for Smoking Control, Self-Efficacy for Alcohol Control, Partner Interaction Questionnaire, Motivation and Confidence contemplation ladder, social network size questionnaire, social engagement questionnaire, Interpersonal Support Evaluation List, Cessation Support from Partner or Buddy, and participant feedback interviews.

5.4 Individually Identifiable Health Information:
HIPCO file and HIPAA authorization form uploaded.

5.5 Use of radiation*:*

N/A

5.6 Use of Center for Magnetic Resonance Research*:*

N/A

6.0 Data and Specimen Banking

N/A

7.0 Sharing of Results with Participants

No data of this nature is collected or shared with participants.

8.0 Study Duration

8.1 Describe:

- The study duration for participants is 26 weeks.
- Enrollment is scheduled to end on March 31, 2018.
- Study procedures are expected to end by September 20, 2018 and data analysis before study end on March 31, 2019.

9.0 Study Population

9.1 Inclusion Criteria:

The study population is homeless adults who smoke cigarettes and drink alcohol. Homeless individuals are considered to be undervalued, often disenfranchised and are vulnerable due to their disadvantage in the distribution of social goods and services including income, housing, and healthcare. This study specifically targets homeless to learn how to address the healthcare disparities they face with lack of access to smoking cessation interventions and lack of research identifying successful smoking cessation strategies that work for homeless individuals wishing to quit smoking.

Individuals must meet the following criteria to be considered for study inclusion:
• Currently homeless (as defined in the Stewart B. McKinney Act passed by the US congress in 1987)
• Smokes > 5 cigarettes per day in past 7 days
• Smoked at least 100 cigarettes in lifetime
• AUDIT score ≥5
• Aged 18 years or older
• Willing to attend study sessions and follow other study protocol

9.2 Exclusion Criteria:

Individuals will be excluded for the following reasons:

• Use of smoking cessation medications or interventions in last 30 days
• Unstable medical illness that requires immediate medical care
• AUDIT score <5 or >27
• Pregnancy or other NRT contraindications
• Current history or in past 6 months of psychotic disorder or major depressive disorders that is not stable on treatment for past 3 months (as determined by the study psychiatrist)
• Cognitive impairment (as measured by the Short Blessed Test)

9.3 Screening:

To make screening and participation convenient for participants, all study visits occur at local homeless shelters. Interested individuals complete an eligibility survey administered by study staff to determine if they are eligible to enroll. The

10-item AUDIT scale is used to screen for alcohol use disorders with scores less than 5 indicating abstinent or low-risk alcohol users and a score over 27 indicative of hazardous use or alcohol dependence. The Short Blessed Test will be administered to determine cognitive capacity to participate. The 7-item Psychotic Disorders and Mood Disorder with Psychotic Features scale of the Mini International Neuropsychiatric Interview (MINI) is administered to screen for psychotic disorders. Those who screen positive for psychotic disorders or major depression may be enrolled provided they have been stable in treatment for past three months. This determination is be made by the study Psychiatrist, Dr. Sheila Specker, who oversees screening and necessary referrals for these psychiatric disorders. To be enrolled in the study, participants must be able to meet study staff at designated homeless shelters. Individuals may screen for eligibility up to five times with a minimum one month window between screenings. This allows those deemed ineligible due to unstable medical conditions the ability to potentially enroll once their health is stable. Eligible individuals are scheduled for a follow-up visit to enroll and be randomized to a study condition.

10.0 Vulnerable Populations

10.1 Vulnerable Populations: *Identify which of the following populations will be involved in this study. (You may not include members of the populations below as participants in your research unless you indicate this in your inclusion criteria above.)*

☐ Children
☐ Pregnant women/Fetuses/Neonates
☒ Prisoners
☒ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☒ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☒ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher

☐ Students of the researcher

☐ None of the above

10.2 Adults lacking capacity to consent and/or adults with diminished capacity to consent:

Justification for inclusion of population:

The study specifically targets homeless adult men and women some of whom are mentally ill, chemically dependent, members of a minority racial and/or ethnic group, and clearly from economically and often educationally disadvantaged populations. The specific aims of the study are to identify effective methods to assist homeless individuals interested in quitting smoking and drinking alcohol with the understanding that methods that are effective in the general public may not be effective with individuals facing the challenges of homelessness as well the life challenges contributing to their homelessness - mental illness, substance abuse, structural racism, and lack of economic resources and education.

The study has numerous validated assessments that are administered as part of the eligibility screening process and the weekly data collection survey process that assess for ability and competency to enroll in the study and to maintain participation once enrolled. Assessments include assessing for cognitive ability (Short Blessed Test), alcohol withdrawal (Clinical Institute Withdrawal Assessment of Alcohol Use, Revised), physical health (documentation of hospital and emergency room visits), mental health (PHQ-9, MINI Anxiety, MINI Psychotic Symptoms), suicidal ideation (Columbia Suicide Severity Rating Scale), current alcohol use and breathalyzer testing to ensure potential and current participants are capable and able to enroll and participate in the study tasks.

We minimize the risks by administering numerous assessments at eligibility screening and at each study session to ensure that at each study visit the participant is coherent, medically and psychologically stable, and not impaired by alcohol or alcohol withdrawal.

10.3 Additional Safeguards:

The study does not enroll pregnant women, does not involve neonates, prisoners or individuals under the age of 18.

11.0 Local Number of Participants

11.1 Local Number of Participants to be Consented:

We plan to enroll a minimum of 428 to allow data analysis with a maximum enrollment of 645 participants.

12.0 Local Recruitment Methods

12.1 Recruitment Process:

Study participants are recruited from homeless shelters and facilities in the Minneapolis/St Paul area that serve homeless adults. Homeless shelters include Dorothy Day Center, Salvation Army Harbor Light, United Gospel Mission, Naomi Family Center, Emma Norton Center, Our Savior's Shelter, St. Stephen's Shelter, and Simpson House. Organizations serving homeless adults include the Catholic Charities Opportunity Centers, Listening House, the Veteran's Service Center, Hennepin and Ramsey County detoxification centers, Sharing and Caring Hands, Higher Ground and the Hennepin County Healthcare for the Homeless programs. Recruiting from multiple homeless shelters and service providers make the study more accessible for participants and ensures a more representative sample.

Study staff post recruitment flyers with tear-off tabs that contain the study phone number and email and hand out half-page flyers to individuals who express interest in the study the above-listed sites.

12.2 Source of Participants:

Participants are recruited from homeless shelters and organizations providing services to homeless adults through face-to-face contact and from recruitment flyers with the study phone number and email address to contact the study.

12.3 Identification of Potential Participants:

Potential participants self-identify in response to posters and to the study staff during outreach at selected sites. Interested individuals complete an eligibility survey that is administered by study staff to determine if they meet the inclusion requirements of the study.

12.4 Recruitment Materials:

The study uses two types of print materials to recruit. One is a full page (8 ½" x 11") poster with tear-off tabs at the bottom. These are posted on the walls of various homeless shelters and service organizations that serve homeless adults. The other is a half-sheet (8 ½" x 5 ½") flyer that is handed to individuals expressing an interest in the study at the various homeless shelters and service organizations that serve homeless adults (as listed in 12.1 above).

12.5 Payment:

Participants are compensated at each study visit they attend. Compensation varies depending on the time the visit is expected to take and the data that is collected at that visit. Compensation includes gift cards (Visa and/or American Express) and small incentives. Incentives include bus tokens, backpacks, pocket calendars, water bottles, note pads, word find book games, Subway gift cards ($5), and playing cards. Participants are also offered a raffle draw during the first 12 weeks of the study when the study treatment (nicotine replacement treatment) is administered and at weeks 16

and 26 when alcohol use is assessed. Raffle prizes include bus tokens (50 chances), $5 Subway gift cards (40 chances) and $10 gift cards (10 chances). Compensation is given at the end of each study visit the participant attends. Over the course of the study participants can earn up to $285 in Visa or American Express gift cards and incentives valued at up to $145 for a total of $430 in total compensation in addition to small raffle winnings. Payments are given only to the study participant, and there are no research experience points awarded.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances:

Participants may be withdrawn from the research without their consent if they harass or otherwise intimidate staff with threats of physical or sexual violence.

13.2 Withdrawal Procedures:

Participants may voluntarily withdraw from the study if they find they are no longer interested in participating or if they will otherwise be unable to continue participation. Those who voluntarily withdraw can return and continue their participation at any point in the future during the 26 week study period. For example, a participant may leave the area for a job, family, or other reason but return and continue participation. When returning, they will re-enter the study at the week they would be at if they had participated continuously. Each study visit has a window of time before and after the ideal date of their visit. Study visits can only be completed during the visit window.

13.3 Termination Procedures:

There is not a procedure for voluntary withdrawals. Those terminated involuntarily are notified in writing at a scheduled meeting to provide the written termination letter and any compensation that may be due to them.

14.0 Risks to Participants

For each risk or set of risks below, include the procedures to be performed to lessen the probability, magnitude, duration, or reversibility of those risks.

14.1 Foreseeable Risks:

There are some risks related to quitting smoking that a participant may experience while in the study. These may include headaches, being uncomfortable, changes in mood, weight gain, and the possibility of going back to smoking. Possible side effects of the nicotine patch may include skin irritation or rash and problems with sleeping. These are generally mild and stop after a few days of using the patch.

Participants are asked by staff at every individual session about side effects from the patch or quitting and any health problem that may interfere with

their ability to use the patch. Participants are given a specific phone number, (612) 625-1850, to report serious side effects and be advised on what to do if the patch or anything related to the study makes then uncomfortable.

Use of the nicotine patch will be under supervision of Dr. Okuyemi. Participants will be prompted to discuss any side effects during follow-up visits and will be given the study office phone number (24-hour coverage) to contact study staff and/or the investigators to report adverse events. We follow the NIH guidelines for reporting adverse events to the IRB. Any problems needing medical attention will be referred to Dr. Okuyemi and the Health Care for the homeless clinics in Minneapolis and St. Paul which are federally qualified community health centers that provide medical care and social services for homeless persons. The patch is discontinued in patients who become pregnant or develop a contraindication. Patients are instructed not to smoke cigarettes during nicotine treatment therapy. Due to the high prevalence of psychiatric and substance abuse co-morbidities in homeless populations, in the proposed study we expect to encounter participates who have one or more of these co-morbidities. It is also possible after enrolling in the study for some participants to develop these co-morbid disorders. Counselors are trained to identify such participants and the study psychiatrist directly oversees the protocol's implementation. For each case the psychiatrist also makes a determination as to whether the participant is mentally stable enough to continue participation in the study.

There are also some risks from stopping alcohol use, however, the study screens out heavy alcohol users to avoid enrolling those at risk for experiencing alcohol withdrawal. Additionally at every study session alcohol use is measured with an alcohol breathalyzer test and the administration of the CIWA, an alcohol withdrawal assessment screen to ensure a participant is not intoxicated or in alcohol withdrawal. If the CIWA indicates an individual is experiencing alcohol withdrawal, study staff walk the person to the on-site medical clinic for further evaluation.

14.2 Reproduction Risks:

Women who are pregnant or breastfeeding are not allowed to enroll in the study because of possible harms the nicotine patch could cause to the fetus. Women of childbearing age must take a urine pregnancy test to ensure they are not pregnant, and if not pregnant must agree to use an effective method of preventing pregnancy while using nicotine patch. Women are instructed to report to staff should they become pregnant while using the nicotine patch and to immediately stop using the patch.

14.3 Risks to Others:

N/A

15.0 Potential Benefits to Participants

15.1 Potential Benefits:

Anticipated benefits of alcohol and tobacco cessation outweigh the minimal risks associated with the nicotine replacement therapy and counseling. Given their already compromised health status, homeless smokers who abuse alcohol are at an extremely high risk of synergistic health effects of tobacco and alcohol. Despite this high disease risk, limited empirical data is available about how to extend effective smoking cessation and alcohol treatment to homeless populations. The current application therefore breaks new ground by assessing methods to extend evidence-based treatments to a vulnerable population. The prevalence of cigarette smoking among alcohol dependent persons is up to 70%, more than three times the rate in general population. In addition to high prevalence of tobacco use in homeless populations, the rates of alcohol and drug abuse are also high in this population. Cigarette smokers drink alcohol more often and more heavily than nonsmokers. Studies have shown that the health consequences of chronic alcohol and tobacco use are synergistic. In one study of 4,928 alcoholics, the high cancer mortality was attributed solely to smoking. Another study by Hurt et al. found a 48% cumulative mortality at 20 years after inpatient alcohol treatment attributable more to tobacco-related diseases than to alcohol.

16.0 Data Management

16.1 Data Analysis Plan:

The primary analysis will be based on an intention to treat (ITT) analysis, i.e., participants will be analyzed in the treatment to which they were randomized. The intervention effects for the primary outcomes of week 26 biochemically verified 7-day abstinence from cigarette smoking (Hyp 1) and week 26 90-day abstinence from alcohol consumption (Hyp 2) will be tested using Chi-square tests. Any participants lost to follow-up will be classified as treatment failures (i.e. smoker or drinker). Bonferroni procedures will be used to control for experimentwise Type I error rate. Abstinence rates and corresponding 95% confidence intervals will be estimated and summarized using appropriate tabular and graphical methods. Supportive analyses will examine baseline variables including demographic (age, sex, income, education), nicotine dependence, withdrawal symptoms, motivation and confidence, self-efficacy, social support, perceived stress, and depressive symptoms in terms of their relationship to study outcomes. Analyses accounting for these measures will be conducted using multiple logistic regression including intervention groups as controlled factors. Thus we can assess whether the main conclusions from the primary analysis are robust for the inclusion of these baseline variables. For hypothesis 3, Fisher exact test will be used to compare the biochemically verified 7-day smoking abstinence rates at week 26 follow-up between the participants who receive the Intensive Smoking intervention (IS) and participants who receive Usual Care (UC). Supportive analysis will be conducted using multiple logistic regression including the intervention group as predictor adjusting baseline covariates to assess whether the result from secondary analysis is robust for

the inclusion of baseline covariates. Analyses for exploratory aims: To examine how smoking cessation, alcohol abstinence, smoking reduction, and alcohol reduction at weeks 12, 26, and 52 follow-up relate to the psychosocial factors, such as level of depression, hopelessness, and perceived stress, other substance abuse, opportunities for employment and housing and overall health, separate repeated measures logistic regressions with generalized estimating equations (GEE) or linear mixed models that accounts for the repeated measures structure of the data will be used to examine the associations between each individual psychosocial predictors and smoking or alcohol outcomes at weeks 12, 26, and 52 follow-ups. Interactions terms between these factors and intervention indicators will be further tested in the above models. Model validation will use analytic and graphical techniques to check assumptions of linearity, homoscedasticity, multivariate normality, and independence of residuals. Descriptive statistics will be used to summarize and ANOVA or Chi-square tests will be used to examine participants' perceptions of acceptability and usefulness of components of the various interventions.

16.2 Power Analysis:

We will enroll 15% more than the calculated sample size to accommodate a higher attrition than that from PTQ1.								
	Usual Care (UC)	Integrated Smoking and Alcohol Intervention (IS+A)	n=284/arm N=645 need to be enrolled	n=260/arm N = 600 need to be enrolled	n=239/arm N=550 need to be enrolled	n=217/arm N = 500 need to be enrolled	n=195/arm N=450 need to be enrolled	n=173/arm N = 400 need to be enrolled
	Abstinence rates from cigarettes smoking (Hypothesis 1)		Power for Hypothesis 1: IS+A vs. UC ($\alpha = 0.025$)					
Target Scenario	4%	18%	99%	99%	99%	99%	98%	97%
Other Scenarios	4%	16%	99%	99%	98%	97%	95%	93%
	4%	14%	97%	96%	94%	91%	87%	82%
	4%	12%	88%	85%	82%	77%	71%	64%
	Abstinence rates from alcohol (Hypothesis 2)		Power for Hypothesis 2: IS+A vs. UC ($\alpha = 0.025$)					
Target Scenario	10%	32%	99%	99%	99%	99%	99%	99%
Other Scenarios	10%	21%	90%	87%	84%	79%	74%	68%
	10%	19%	76%	71%	67%	62%	56%	50%

16.3 Data Integrity:

Participant enrollment, study participation, and retention are tracked on an Excel spreadsheet as well as in REDCap, the study database. All eligibility screening forms are completed on paper and then entered into the REDCap database. Participant data is entered into a REDCap database from both paper forms completed at the beginning of the study and from direct data entry in the field during study visits. The spreadsheet and REDCap are regularly reconciled for quality control.

17.0 Confidentiality

17.1 Data Security:

Data will be stored in REDCap databases. Data for this study will be entered into interactive, relational REDCap databases, which use a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

Consent forms or other study information will not be placed in any participant medical, employment or education records..

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring.

A Data Safely Monitoring Board (DSMB) was established in January 2016. The first meeting was held in April 2106. The qualification for members includes research knowledge and experience with tobacco cessation, homeless adults, health disparities with vulnerable and underserved populations and statistical methodologies. Members were selected based on these qualifications, their interest, and their availability to attend meetings and review data.

DSMB members determine the frequency of meetings based on the reports provided them. Each report contains a detailed recruitment update that includes current enrollment and recruitment, consort diagram, and a target vs. actual recruitment chart; a description of the study sample by treatment group; a safety assessment including adverse events and serious adverse events by treatment group; a data collection update including counseling treatment visits and weekly visits by treatment group; and a list of protocol violations.

DSMB members monitor enrollment numbers and review blinded treatment data to ensure significant sample size and when necessary, to propose design

changes to ensure significant outcomes. Monitoring is accomplished through regular meetings to share data to understand any enrollment, participant safety, or unforeseen issues affecting study outcomes and deadlines that may require design, endpoints or outcomes. The monitors are responsible to review the data and propose sustainable solutions to maintain the research goals and outcomes. The reports compiled for DSMB members are shared with co-investigators with treatment group data blinded.

Data Safety Monitoring.

Study participants are asked to report any adverse events they have experienced during their study participation at each study visit. Participants are asked if they were hospitalized or sought emergency medical care since their last visit. All hospitalizations and emergency room visits and the reason are recorded and paper by the study team and entered into REDCap, the study database. The study PI, a medical doctor with extensive tobacco cessation research experience, reviews all adverse events. All adverse events and serious adverse events are regularly report to the DSMB as noted above after a review by the study statistician to ensure if any harms are occurring. Currently there are no identified conditions that could trigger an immediate suspension of work. Nicotine replacement products have been on the market and proven to be safe for a number of years. This is the second phase of a study in the same population where no serious safety issues have occurred.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

All participant contact is conducted by trained research staff and occurs in a private office or a dedicated space that affords participant privacy.

19.2 Access to Participants:

The research does not involve collecting data from any kind of participant record.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury:

N/A.

20.2 Contract Language:

N/A.

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

Consent will take place at homeless shelters and service organizations serving homeless adults. After completing the eligibility survey prospective participants will be notified of their eligibility and scheduled to enroll at the next available study visit. Participants are assessed at every study visit for

ability to participate. All participants take an alcohol breathalyzer test at every study visit and must test below .08 in order to complete the study visit. Participants are also assessed at every study visit for cognition and for suicidal ideation. Staff assess for incoherence, disorganized speech, or marked loosening of associations and administer the Short Blessed Test if concerned. If the participant does not pass the Short Blessed Test, they are rescheduled. Consent is obtained in writing.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained):

N/A

21.3 Non-English Speaking Participants:

Non-English speakers are not enrolled in the study.

21.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

Individuals must be at least 18 years old to enroll.

21.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

All participants take an alcohol breathalyzer test at every study visit and must test below .08 in order to complete the study visit. Participants are also assessed at every study visit for cognition and for suicidal ideation. Staff assess for incoherence, disorganized speech, or marked loosening of associations and administer the Short Blessed Test if concerned. If the participant does not pass the Short Blessed Test, they are rescheduled.

21.6 Adults Unable to Consent:

N/A

22.0 Setting

22.1 Research Sites:

As noted in other sections above, study participants are recruited from homeless shelters and facilities in the Minneapolis/St Paul area that serve homeless adults. Homeless shelters include Dorothy Day Center, Salvation Army Harbor Light, United Gospel Mission, Naomi Family Center, Emma Norton Center, Our Savior's Shelter, St. Stephen's Shelter, and Simpson House. Organizations serving homeless adults include the Catholic Charities Opportunity Centers, Listening House, the Veteran's Service Center, Hennepin and Ramsey County detoxification centers, Sharing and Caring Hands, Higher Ground and the Hennepin County Healthcare for the Homeless program. All research procedures are performed at the sites.

23.0 Multi-Site Research

N/A

24.0 Resources Available

24.1 Resources Available:

The study does not have a student investigator. The feasibility of the recruiting numbers was determined by the results of the PTQ I study. However, we have found it necessary to adjust the original proposed numbers due to a large number of individuals unable to meet the criteria for alcohol use. The new numbers were calculated by the study statistician, the NIH project officer and the DSMB. The study began enrolling participants in January 2015 and expect to complete enrollment at the end of March 2018 which leaves and additional year for follow-up, data cleaning and analysis and development of manuscripts.

The study staff conduct the research in homeless shelters and service organizations in Minneapolis and St Paul. When not working in the shelters, they work from study offices at UROC in Minneapolis and a commercial site in downtown St Paul, both of which are close to the two primary homeless shelters serving large number of homeless adults. All study sites have medical and psychological services available onsite through Healthcare for the Homeless. Staff also carry referral information for Hennepin and Ramsey county crisis hotlines and the national suicide hotline for participants who screen for suicidal ideation. The study psychiatrist is on-call for telephone consultations and the study has written procedures for calling emergency services if the on-site healthcare clinic is unable or unavailable to assist.

New staff complete all required trainings before working on the study and read the study procedures and become familiar with the study data collection forms and tools. Once in the field with the study team, they observe how the study is conducted first and then are trained to administer the study surveys. The study team observes new staff in administering surveys until they are determined to be proficient and able to conduct the field work without supervision. The study team meets weekly to discuss study issues and to review protocols and procedures to ensure fidelity to the protocol.

25.0 References

Include references to any scholarly articles or other materials used to discuss the background for the study or to justify any proposed procedures.