ClinicalTrials.gov: NCT04445662

TITLE: Financial incentives for homeless smokers: A community-based RCT

PRINCIPAL INVESTIGATOR: Travis P. Baggett, MD, MPH

GRANT NUMBER: R01 CA235617 (National Cancer Institute, National Institutes of Health)

VERSION DATE: December 7th, 2023

I. BACKGROUND AND SIGNIFICANCE

A. Historical background

An estimated 68-80% of homeless adults are cigarette smokers[1-6], in contrast to the 18% prevalence in the U.S. general population.[7] The health impact of this disparity is substantial. Obstructive lung disease is more than twice as prevalent among homeless individuals than in the US general population,[3] contributing to higher rates of death due to COPD and other respiratory causes.[8-10] Heart disease is a major cause of death among homeless adults,[11, 12] and several studies have shown higher rates of mortality due to circulatory system diseases among homeless persons in comparison to non-homeless counterparts.[8-10, 12, 13] In a series of epidemiologic studies of 28,033 homeless adults in Boston, we found that one-third of incident cancers in this cohort were smoking-attributable, and the age-adjusted lung cancer incidence and mortality rates were over 2-fold higher than in Massachusetts adults.[14] These findings contributed to 3- to 5-fold higher rates of death due to any tobacco-attributable cause relative to rates in the Massachusetts general population.[15]

Homeless smokers are interested in quitting.[2, 16-19] In 2002, Butler et al. reported that 56% of homeless smokers were contemplative about quitting and 17% were in preparation to quit; the level of interest in smoking cessation programs was not significantly different from that seen in low-income non-homeless smokers.[16] In the same year, Connor et al. found that 37% of homeless smokers were ready to quit within the next 6 months.[2] In 2004, Arnsten et al. reported that 44% of homeless smokers were somewhat or very interested in smoking cessation counseling, and 19% were either preparing or trying to quit.[18] In a nationwide study of homeless and non-homeless community health center patients in the United States, we found that currently and formerly homeless smokers did not differ from never-homeless smokers in their past-year desire to stop smoking.[19] In a 2014 survey of 306 homeless smokers at Boston Health Care for the Homeless Program (BHCHP), 62% of participants had intentionally quit smoking for at least 24 hours in the past year and 85% planned to quit smoking in the future, including 24% who planned to do so in the next month.

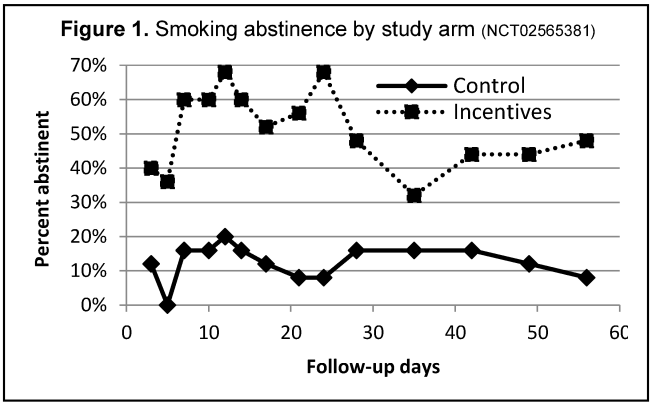
Despite their interest, few homeless smokers are able to quit and self-efficacy for quitting may be low.[18] Baggett and Rigotti found a quit ratio (the proportion of ever-smokers who are former smokers) of 9% in a national sample of homeless adults,[1] a figure one-fifth of that observed in the US general population.[20] The pervasiveness and social acceptability of smoking in the setting of homelessness[17, 21] may be one explanation for the low success rate. Homeless smokers are continuously confronted with social cues to smoke. In a survey of homeless smokers in Dallas, participants reported contact with a mean of 43 other smokers each day.[22] Additionally, homeless smokers are a vulnerable subset of homeless individuals; they are more likely to have histories of childhood adversity, physical or sexual assault, and alcohol or drug use problems.[1] In comparison to non-homeless smokers, homeless smokers begin smoking at

an earlier age and smoke more heavily, with a tendency toward higher levels of nicotine dependence.[16] Many homeless smokers report difficulty accessing cessation therapies,[17] which may be due in part to the high rates of lacking health insurance and lacking a usual source of care in this population.[23]

Few RCTs of smoking cessation interventions have been conducted for homeless smokers. In 2001, an RCT comparing usual care to multicomponent smoking treatment consisting of 2 counseling strategies coupled with nicotine replacement therapy (NRT) in homeless substance-dependent smokers in a residential rehabilitation program resulted in 10-12% abstinence rates at 1 year in the intervention groups compared to 0% in the usual care group.[24] A 2004 pilot RCT comparing 2 motivational interviewing (MI) protocols coupled with NRT for homeless smokers showed modest 7-day abstinence rates at 26 weeks (8.7% and 17.4%).[25] In 2009-10, the largest RCT of homeless smokers to date randomized 430 participants to nicotine patch treatment with or without MI.[26] Point-prevalence abstinence rates at 6 months were similarly low for both arms (9.3% vs. 5.6%, p=0.15).[26] The modest results of these high-quality studies suggest that the optimal approach to promoting smoking cessation among homeless people remains uncertain.

B. Preliminary data

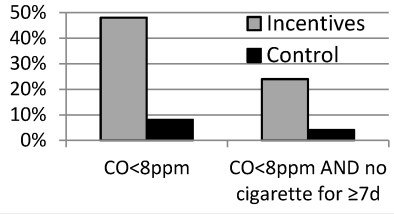
In October 2015-June 2016, we conducted a pilot RCT of financial incentives for smoking abstinence among homeless smokers at BHCHP.[27] Participants were offered 8 weeks of transdermal nicotine patches and 8 15-minute sessions of behavioral counseling, with (N=25) or without (N=25) escalating financial rewards for brief smoking abstinence, defined as an exhaled CO level <8 ppm.[28] After randomization, participants were asked to make 14 assessment visits over 8 weeks: 3 times per week during weeks 1-2, 2 times per week during weeks 3-4, and once per week during weeks 5-8. Control arm participants received a $10 payment at each visit, regardless of whether they were abstinent. Incentive arm participants received a payment only if they were abstinent. Payments began at $15 and increased in $5 increments with each successive abstinent measurement, up to a maximum of $35. Non-abstinence or non-attendance resulted in no payment and reset subsequent payments to the starting value of $15. Payments were issued electronically in real-time onto study-supplied debit cards that could be used at any retail outlet. The primary outcome was a repeated measure of CO-defined abstinence (CO <8 ppm) across the 14 assessment visits. Sensitivity analyses incorporated self-reported abstinence duration.



Two-thirds of eligible individuals participated in the RCT, and we reached our target enrollment within 6 months. Participants attended a median of 10 (of 14) assessment visits, with 98% attending ≥1 visit and 78% attending ≥7 visits. Across all 14 time points, CO-defined smoking abstinence was substantially higher in the incentives arm than in the control arm (ranges: 32-68% vs. 0-20%; overall OR 7.28, 95% CI 2.89-18.3; Figure 1). At 8 weeks, 48% of incentive arm participants and 8% of control arm participants had an exhaled CO <8 ppm (P=0.004; Figure 2). In a sensitivity analysis incorporating self-report of not smoking all or part of a cigarette in ≥7

days, the relative effect of the intervention was preserved but the percentages meeting this definition of abstinence were lower (24% vs. 4%; Figure 2). Incentives appeared to have a negligible effect on more stringent definitions of abstinence (i.e. not even a puff of a cigarette in ≥7 days), and post-treatment abstinence was not assessed. Incentive arm participants made 2 more 24-hour quit attempts per month than control participants (p=0.03) but did not differ with respect to NRT use or counseling attendance. Confidence to quit and importance of quitting, measured serially throughout the trial, did not differ by study arm. Incentive arm participants earned an average of $180 (of $440 possible) over 8 weeks.

Figure 2. Abstinence at 8 wks (NCT02565381)



C. Study rationale

Our pilot RCT results, together with the findings of prior non-randomized[29] and single-group[30] studies, suggest that financial incentives are a promising approach for reducing smoking in this vulnerable population while pointing toward the need for modifications to improve the duration of on-treatment abstinence and an assessment of post-treatment effects. In addition, little is known about mechanisms of action and contextual factors that may influence on-treatment and post-treatment response to financial incentives in the setting of homelessness.

Initially we had planned to implement an augmented version of our pilot trial. Participants were to be offered the opportunity to attend frequent study visits and receive payments for short-term smoking abstinence, confirmed via a reusable CO monitoring device into which participants would deliberately and forcefully exhale in an indoor space. Unique to the current trial, we would have also assessed long-term smoking abstinence using urine anabasine testing at various timepoints. In view of the ongoing COVID-19 pandemic, we revisited the safety of these study procedures and decided that modifications were needed in order to minimize the risk of COVID-19 transmission among participants and staff.

The chief modification was to remove CO breath testing. However, relying solely on urine anabasine testing for abstinence verification was not desirable as this test does not provide results at the point of care. As a result, the trial would lose the opportunity for immediate reinforcement payments, which are critical in contingency management. As an alternative, we now propose using point-of-care salivary cotinine testing to verify smoking abstinence. Cotinine is a major metabolite of nicotine that can be detected in saliva and urine.[31] Saliva testing is less intrusive than urine testing and would lead to a lower transmission risk of COVID-19 compared to CO breath testing. Additionally, saliva cotinine has a half-life of about 16 hours, which is similar to urine anabasine and much longer than that of breath CO.[32] Therefore monitoring visits would not need to occur as frequently, reducing in-person contact for both participants and study staff.

One complication of switching to cotinine testing is that nicotine replacement therapy (e.g. nicotine patches, lozenges, etc.) cannot be used by participants as a smoking cessation aid as this will interfere with cotinine measurement. To align with current standards of care for treating tobacco use,[33] we felt it was important that participants were offered some type of cessation medication during the study. Based on available evidence and updated recommendations from the American Thoracic Society,[34] we concluded that varenicline was the best option. Varenicline

is an FDA-approved prescription smoking cessation medication[33] that acts as a partial agonist/antagonist at nicotinic receptors, easing withdrawal symptoms while also blocking the rewarding effects of nicotine from cigarettes.[18] Varenicline is now strongly recommended as a first-line smoking cessation medication in virtually all patient populations.[34] Research suggests that varenicline is superior in producing short-term and long-term abstinence compared to bupropion[35] while also producing higher continuous abstinence rates than NRT.[36] When paired with counseling, varenicline is the most effective smoking cessation medication available.[37] Varenicline has also been shown to be safe and effective in at-risk populations, including those with comorbid psychiatric conditions,[38] alcohol use disorder [39] and substance use disorders.[40, 41] To date there has been limited research on the use of varenicline in homeless populations.[42] Therefore, the results of the current study may provide further insight on the uptake of and adherence to varenicline in a homeless population.

II. SPECIFIC AIMS

To address the above gaps in evidence, we will conduct a community-based RCT of financial incentives for smoking abstinence among adult smokers at BHCHP. Recognized as a leader in homeless health care, BHCHP serves 12,000 currently and formerly homeless patients annually throughout greater Boston.[43] We will randomize 180 participants recruited from 3 BHCHP sites: a shelter clinic, a day center clinic, and a medical center clinic. All participants will be offered 12 weeks of varenicline, 5 sessions of tobacco coaching, and 10 cotinine monitoring visits over a 12-week period. Participants randomized to the financial incentives arm (n=90) will receive escalating debit card payments (range $25-$70) at each monitoring visit for saliva cotinine levels <30 ng/ml. Control arm participants (n=90) will receive a fixed payment ($10) at each monitoring visit regardless of their saliva cotinine level. We will use an embedded-experiment mixed methods design,[44] where qualitative ('qual') data collection is embedded within a larger quantitative ('QUAN') RCT with the following specific aims:

Aim 1. (QUAN) To determine the effect of the financial incentives intervention on cotinine-verified 7-day smoking abstinence at **A)** the end of treatment (12 weeks) and **B)** 12 weeks after treatment (24 weeks).

Hypotheses: Incentive arm participants will have significantly greater cotinine-verified 7-day smoking abstinence than control arm participants at **A)** 12 weeks and **B)** 24 weeks.

Aim 2. (qual) To assess why, how, and under what circumstances homeless smokers **A)** achieve abstinence in response to financial incentives and **B)** maintain abstinence after incentives are stopped.

Interviews with participants at **A)** 12 weeks (N=30) and **B)** 24 weeks (N=20) will examine cognitive ('why?'), procedural ('how?'), and contextual ('under what circumstances?') dimensions of their response to financial incentives to generate hypotheses about potential mechanisms for on-treatment and post-treatment effects and to inform modifications of the intervention for future use.

III. SUBJECT SELECTION

A. Inclusion and exclusion criteria

To be eligible to participate, individuals must meet **all** of the following criteria:

1) Aged ≥18 years old, assessed by self-report and verified by date of birth.
   Rationale: We wish to focus only on adult smokers since adolescent smokers present unique issues that merit separate consideration.
2) Lifetime smoker of ≥100 cigarettes with current daily smoking of ≥5 cigarettes/day, verified by a saliva cotinine level ≥30 ng/mL.[28]
   Rationale: In order to document smoking abstinence via saliva cotinine levels, trial participants must smoke a sufficient number of cigarettes per day at baseline to be above the accepted threshold of 30 ng/ml for determining smoke exposure.
3) Ready to try to quit smoking within the next 3 months, assessed by self-report.
   Rationale: We wish to focus on smokers interested in quitting in the near future in order to better isolate a treatment effect.
4) Proficient in English, assessed with items asking about native language and self-reported comfort communicating in English among non-native speakers.
   Rationale: We do not have the resources to develop study materials or conduct in-person counseling in languages other than English.
5) Currently or formerly homeless, assessed by self-report and defined as having ever stayed in an emergency shelter, transitional shelter, abandoned building, place of business, car or other vehicle, church or mission, hotel or motel, or anywhere outside, or having ever stayed in somebody else's house, apartment/condominium, or room due to not having their own place to stay.
   Rationale: BHCHP and most HCH programs nationally continue to serve patients after they have gained housing. Additionally, currently and formerly homeless people smoke at similarly high rates,[19] and our epidemiologic analysis of tobacco-attributable cancer and mortality disparities experienced by BHCHP patients included both currently and formerly homeless individuals.[15, 45]
6) Have a primary care provider (PCP) within the BHCHP system.
   Rationale: This will help ensure that we can communicate efficiently with participants' PCPs via secure, EHR-based messaging systems regarding the safe use of varenicline for smoking cessation.

Individuals will be excluded if they meet **any** of the following criteria:

1) Unable to provide informed consent, assessed with knowledge questions about the material presented during the informed consent process that individuals must correctly answer before providing consent to participate.
   Rationale: Participants must have a clear understanding of what is involved in the study prior to enrolling.
2) Report a history of an allergic reaction to varenicline.
   Rationale: Varenicline is a treatment component in both study arms.
3) Currently pregnant, planning to become pregnant, or breastfeeding.
   Rationale: There is limited information on the safety of varenicline in pregnant women.[46,47]

4) Past-month suicidal ideation with plan or intent**,** or past 12-month history of suicidal behaviors or attempts, based on the primary care screening version of the Columbia Suicide Severity Rating Scale (C-SSRS).[48]
   Rationale: Due to past reports of suicidal ideation in patients taking varenicline and limited research on the safety of prescribing varenicline to individuals with recent suicidal ideation or behaviors,[49, 50] we do not believe it is appropriate for these patients to participate in the study.
5) Self-reported psychiatric hospitalization in the past 3 months.
   Rationale: Varenicline carries a caution label for neuropsychiatric events. There is also limited research on the use of varenicline in patients with unstable mental illness. Hence, we do not feel that it is appropriate to include patients with a recent psychiatric hospitalization in the study.[41, 49, 51]

We will not exclude individuals who use alcohol or other drugs, as long as they meet all of the above eligibility criteria. This decision was made because our prior survey of homeless smokers in Boston suggested that limiting the trial to individuals who do not use other drugs or alcohol would considerably narrow the pool of potentially eligible participants and would severely limit the generalizability of our findings. Concomitant drug and/or alcohol use is common among homeless smokers,[1] and smoking interventions for this population must contend with that reality in order to be applicable. In our pilot RCT, we found that drug and alcohol use, assessed serially over 8 weeks, did not change among participants assigned to receive financial incentives for smoking abstinence. Furthermore, evidence suggests varenicline is both safe and effective in patients with a history of substance use disorder.[40,38, 40] Because of the potential importance of this issue, we again plan to assess drug and alcohol use with a validated instrument at the beginning, middle, and end of the trial, and to conduct interaction analyses to determine whether drug and alcohol use severity modify the effect of the intervention.

B. Source of subjects and recruitment methods

This study will be registered with ClinicalTrials.gov prior to the recruitment and enrollment of human subjects. All participants will be recruited from BHCHP clinical sites. BHCHP does not have its own IRB but instead will rely on the Mass General Brigham Human Research Committee for IRB review through a reliance agreement initiated through SMART IRB. In addition to being a faculty physician-investigator at Massachusetts General Hospital and Harvard Medical School, the study PI has over 20 years of clinical experience with homeless patients and more than 13 years of research experience relating to the health of homeless people. He has been a staff physician at BHCHP since 2008 and was named the Director of Research at BHCHP in 2017.

Recruitment of study participants will occur at up to 3 venues; however, initial efforts will focus on the first of these sites:

a) Medical center venue: Jean Yawkey Place, adjacent to Boston Medical Center, is the BHCHP headquarters facility where medical, behavioral health, and dental clinics operate 5 days per week with an on-site pharmacy and medical respite unit. Compared to other BHCHP locations, Jean Yawkey Place has the highest volume of patients, the most space, and the greatest flexibility in space configuration. This will allow study personnel to conduct in-person participant recruitment while practicing COVID-appropriate social distancing and prioritizing the health and well-being of both participants and study staff.

Depending on the status of the COVID-19 pandemic, recruitment may later expand to two additional locations when safe to do so:

b) Shelter venue: Pine Street Inn is a 470-bed shelter serving both men and women where BHCHP operates a medical clinic 7 days per week in the men's shelter and 6 days per week in the women's shelter.

c) Day center venue: St. Francis House is a multiservice day center for homeless people where BHCHP operates a medical clinic 5 days per week.

Study participants will be recruited through five methods:

a) Self-referral: Study staff will be stationed in heavily trafficked areas within the recruitment sites at prespecified times each week. We anticipate that a general awareness of the study due to study staff presence and word-of-mouth will encourage prospective participants to approach study staff and undergo eligibility screening if interested.

b) *Proactive outreach:* BHCHP has a comprehensive EHR system (Epic) that prompts providers to assess tobacco use at every clinical encounter, facilitating determination of smoking history and current smoking status. Individuals with a BHCHP PCP who have been seen in a BHCHP clinic in the past year and who were current smokers at the time of their most recent clinical encounter will be approached in person at BHCHP clinical sites if they have a scheduled appointment or contacted proactively via phone (if they have listed contact information) by a research coordinator and screened for eligibility to participate. The BHCHP Chief Medical Officer has approved this recruitment strategy on behalf of all primary care providers at BHCHP clinical sites, who will in turn be notified about this recruitment approach (see attached letter of approval).

c) Referrals from Boston Health Care for the Homeless Program (BHCHP) clinical staff: Physicians, advanced practitioners, nurses, and other clinical staff at each BHCHP site routinely screen all patients for tobacco use. We will inform BHCHP staff about the RCT through program-wide presentations and emails and encourage them to refer all current smokers for eligibility screening at one of the recruitment sites and/or securely message study staff about potentially eligible patients who may be good candidates for outreach screening as described in section (b).

d) Recruitment flyers: We will post and distribute study advertisements at BHCHP sites to facilitate patient self-referrals for eligibility screening.

e) Rescreening of previously screened participants: Participants who have previously been screened have also consented to letting study staff keep their data. Participants who were previously screened and ineligible due to time-varying factors such as not having seen their PCP in the past year, or participants who previously screened as eligible but did not enroll within two weeks of screening (see section V.A.2) will be periodically recontacted and invited to screen again to determine eligibility if they granted study staff permission to be contacted again. We will not contact participants who had previously told study staff that they did not wish to be contacted.

Following screening, eligible individuals will be invited to attend a study enrollment visit to complete written informed consent and a baseline survey.

IV. SUBJECT ENROLLMENT

A. Methods of enrollment

Participant screening, enrollment, and randomization will take place over the course of 3 visits:

1) Screening visit: Individuals recruited through the above methods will be screened for study eligibility. Prospective participants who approach study staff during prespecified open-screening sessions at clinic sites will complete the entire eligibility screen in-person. Prospective participants who call study staff directly or who are proactively contacted for recruitment over the phone will be given the option to complete the eligibility screener questions over the phone and then complete the saliva cotinine test in-person at JYP (see section V.A.). We anticipate screening up to 1000 people in order to reach our target of 180 randomized participants.

2) Enrollment visit: Individuals who are eligible for the study will be invited to attend a study enrollment visit for written informed consent, collection of demographic and contact information and assessment of baseline measures.

3) Randomization and baseline clinician visit: Individuals who complete the enrollment visit and baseline survey will be asked to return for a baseline clinical evaluation by the study clinician. The study clinician will evaluate participants to determine if a varenicline prescription is appropriate and will provide the initial prescription for varenicline in most cases (see section V.A. for details). Concurrently, participants will be randomized to the control arm (N=90) or financial incentives arm (N=90). Randomization will be stratified by housing status (currently homeless vs. currently housed). Following randomization, staff will set up a brief introductory video on a tablet to orient participants to their study arm. Participants without a mobile phone will be provided one with a prepaid voice and text plan to facilitate communication and follow-up (see section V.C. for details).

B. Informed consent procedures

Informed consent will be obtained in person by a research staff person working under the direction of the PI. During the consent process, study staff will ask all potential participants if they would like to speak with a physician. If the participant chooses to speak with a physician, study staff will immediately send a secure message to the PI, Dr. Travis Baggett, who will respond to talk with the participants as soon as possible (within 30 minutes). To ensure that participants have an adequate understanding of the potential risks associated with study participation, all participants will be informed of these risks in plain language on a written informed consent document that will be read aloud to each participant, making no assumption of literacy.

Participants will be informed of the option of not participating in the study and that their decision regarding study participation will in no way impact their ability to receive future services at BHCHP. Following a practice we established in our prior survey work involving homeless smokers and further refined in our pilot RCT for homeless smokers, we will confirm individuals' understanding of the consent materials with basic knowledge questions about the consent document content to ensure that they have the capacity to provide informed consent. Individuals who are able to correctly answer these questions will be asked to sign the paper consent form if

they wish to enroll in the trial. A signed copy will be retained by study staff and a second signed copy of the consent form will be given to participants for their own records.

C. Treatment assignment

Participants will be randomized 1:1 to the control arm (n=90) or the financial incentives arm (n=90). Randomization will be stratified by housing status to ensure balanced representation of housed and homeless individuals across the 2 study arms. The attached Study Schema provides an integrated summary of the screening, enrollment, and randomization procedures along with the components of each study arm and the principal study outcomes.

The 2 study arms are as follows:

1) Control arm (n=90): Participants in this arm will be offered 12 weeks of varenicline and 5 sessions of tobacco coaching. As an attention control to help ensure a similar level of contact to the financial incentives arm, control arm participants will have the option to attend 10 cotinine monitoring visits over 12 weeks during which they would submit saliva samples for cotinine testing and receive a fixed debit card payment, irrespective of the result.

2) Financial incentives arm (n=90): Participants in this arm will be offered 12 weeks of varenicline and 5 sessions of tobacco coaching in a manner identical to the control arm. These participants will also have 10 cotinine monitoring visits over a 12-week period where they will receive debit card payments for saliva cotinine levels <30 ng/ml.

V. STUDY PROCEDURES

A. Study visits and measurements

A complete timeline of study activities is depicted in Figure 3 below. In total, this study will involve a screening visit, an enrollment visit, a randomization and baseline clinician visit, 2 additional clinician visits, 5 tobacco coaching sessions, 10 on-treatment monitoring visits over 12 weeks, and a post-treatment outcome assessment visit at 24 weeks. Participants must complete their enrollment visit within 2 weeks of their screening visit. The randomization and baseline clinician visit must be completed within 4 weeks of enrollment. During this visit, participants will be encouraged to set a quit date for the following week. Participants who are prescribed varenicline by the clinician will attend 2 follow-up clinician visits at weeks 3 and 7 (+/- 1 week). The first tobacco coaching session will occur on participants' quit date and the remaining 4 sessions will coincide with on-treatment monitoring visits at 2, 4, 8 and 12 weeks (or within one week after each of these time points). On-treatment monitoring visits will begin 1 week after the quit date. Selected participants will additionally be asked to participate in qualitative interviews at the end of treatment (12 weeks) and at the end of follow-up (24 weeks). The content and measurements involved in each of these visits are described below.

Figure 3. Study activities timeline

	Pre-Treatment			On-Treatment										Post Treatment
Week:	-2	-1	0	1	2	3	4	5	6	7	8	10	12	24
Screening	•													
Enrollment	•													
Baseline Survey	•													
Randomization		•												
Clinician Visit		•				•				•				
Quit Date			•											
Tobacco Coaching			•		•		•				•		•	
Monitoring Visit[1]				•	•	•	•	•	•	•	•	•	•	
Outcomes Assessment[2]													•	•
Follow-up Survey													•	•
Interview													•	•

Notes: 1) Includes a point of care saliva cotinine test and a brief questionnaire; 2) Includes a second non-point of care saliva cotinine test from J2 Laboratories

Depending on space availability, participant preference, and the safety of having in-person interactions based on the status of the COVID-19 pandemic, study participants may complete surveys, coaching sessions, clinician visits, and qualitative interviews in the following ways: **A) On-site in-person**: Staff may administer the surveys/provide coaching in-person at a private area in the clinic space while adhering to physical distancing guidelines. **B) On-site virtual**: Study staff will set up a tablet in a separate on-site room for participants and administer the survey/provide coaching via Microsoft Teams or Enterprise Zoom. **C) Remote and virtual**: Participants with access to a phone, smartphone, or computer can complete the surveys, coaching sessions, clinician visits, and/or interviews virtually with study staff via phone call, Microsoft Teams, or Enterprise Zoom.

Regardless of how participants complete study visits, the PI, Dr. Travis Baggett, and/or the study clinician will be available to advise study staff and speak with participants as needed. Any questions or concerns raised during the consent or enrollment phase in addition to any issues unrelated to varenicline raised throughout the study will be directed to the PI. Any questions or concerns related to varenicline raised throughout the study will be directed first to the study clinician, with the PI serving as back-up.

1) Screening visit: Participants will be screened for study eligibility through measurement of the specific data variables listed in section VI.A. Participants who are proactively contacted for recruitment or who contact study staff directly will be offered the option to complete the eligibility screener questions over the phone. If their responses to the questions suggest that they are eligible to participate, they will be invited to meet with study staff in person at JYP to confirm their eligibility with a saliva test for cotinine. If the cotinine saliva test is consistent with current smoking, participants will be able to proceed with enrollment procedures. Both the eligibility screener saliva test and all enrollment procedures need to occur within 2 weeks after the participant answered the eligibility screener questions. Eligible participants who complete all components of the eligibility screening in-person during open screening hours will be asked to come back at a later time to complete enrollment procedures (also within 2 weeks).

2) Enrollment visit: The enrollment visit will occur within 2 weeks after completing the screening visit. If more than 2 weeks has elapsed since screening, participants will need to be rescreened before proceeding to enrollment. During the enrollment visit, eligible participants will provide written informed consent. Enrolled participants will then complete a baseline assessment that includes measurement of the specific data variables listed in section VI.A and a demographics/contact form that includes data variables listed in section VI.A. Participants will also be provided with their CT Payer cards (listed below in section XI.A) during this visit upon completion of the baseline assessment survey. Participants will receive $25 for completing the

baseline survey. Prior to randomization visits, CRCs will look up enrolled participants in the BHCHP electronic health record (EHR) and will complete a chart review form (data variables to collect listed in section VI.A). Enrolled participants will then be randomized to a study arm in the manner described above.

3) Randomization and baseline clinician visit: The randomization and baseline clinician visit will occur within 4 weeks after completing the enrollment visit. If more than 4 weeks has passed since enrollment, participants will first need to undergo repeat screening to confirm their continued eligibility, followed by reassessment of baseline survey measures to inform randomization and identify conditions relevant to varenicline use (see below), before being allowed to proceed to randomization. During the randomization visit, study staff will reveal the participant's group assignment and set up the introductory video which will explain the study components and the study schedule. After the introductory video, staff will provide participants with a study cell phone if applicable (see section V.C.). The participant will then be seen by the study clinician, as described in more detail below. During this visit, participants will be encouraged to set a quit date for the following week.[52] Participants will receive $10 for attending this visit.

4) Clinician visits: Participants who are enrolled and interested in varenicline will meet with the study clinician for a maximum of 3 visits. The first visit will occur at the time of randomization, as described above. At the first visit, the clinician will assess health conditions relevant to participants' use of varenicline based on their responses on the baseline survey, their health history as documented in the BHCHP electronic health record, and their self-reported health history discussed during the visit. The clinician will use this information to follow a risk-based varenicline prescribing protocol detailed in section V.B. If the participant is undecided on whether they would like to try varenicline or if approval is needed from the participant's PCP and is still pending, the clinician may delay writing the varenicline prescription for up to 2 weeks following the initial clinician visit. Participants prescribed varenicline at the start of the study will attend 2 on-treatment follow-up clinician visits in conjunction with monitoring visits at on-treatment weeks 3 and 7 (or within 1 week pre or post these timepoints). During these visits, participants will meet with the clinician to discuss varenicline adherence and side effects, as well as to have their prescription refilled, adjusted, or stopped depending on participants' preferences and degree of response and tolerance to the medication. During the week 7 visit, the clinician will also encourage the participant to think about whether they are interested in remaining on varenicline after they finish with their study prescription after 12 weeks. Varenicline will only be prescribed for 12 weeks in this study but can be safely prescribed for up to 24 weeks to increase the chances of long-term abstinences for those who have quit smoking or to further increase chances of quitting.[52] If participants are interested in remaining on varenicline after completing 12 weeks, they will be encouraged to talk to their PCP to determine if continuing varenicline is appropriate for them.

5) Tobacco coaching sessions: Coaching sessions will occur on the participants' quit date and at monitoring visit weeks 2, 4, 8, and 12. To enhance uptake of these services and acknowledge the competing life priorities[53-56] of homeless smokers, participants will receive $15 for each coaching session they attend. Participants can complete coaching sessions up to 1 week after the scheduled date.

a) Session 1: A 30-minute baseline session will coincide with the participants planned quit date. During this session, the coach will assess participants' readiness to quit, deliver a brief smoking

cessation intervention using the “5 A’s” approach (Ask, Advise, Assess, Assist, and Arrange),[57] provide motivational interviewing on the use of varenicline, and introduce the “3-sided triangle” of tobacco addiction.

b) Sessions 2-4: 20-minute follow-up sessions at 2, 4, and 8 weeks will review skills for quitting smoking. The counseling content of these visits will be based on the counseling protocol used in our pilot RCT, which incorporated elements of motivational interviewing and cognitive behavioral therapy, both applied in practical and concrete ways, to help homeless smokers overcome ambivalence about quitting and establish goals for behavior change. The protocol was structured around the American Lung Association *Freedom from Smoking* program theme of addressing the 3 parts of tobacco addiction: physical, mental, and social.[58] Each session includes brief psycho-education in combination with skills-building and practical tips for coping with cravings, emotional triggers, and high-risk social situations, with content tailored to the unique circumstances of homeless people.

c) Session 5: A final 30-minute session at 12 weeks will focus on identifying treatment needs following the study. For participants who have achieved abstinence at 12 weeks, this visit will focus on relapse prevention skills in addition to contingency planning for lapse or relapse. For non-abstinent participants, this visit will focus on motivational enhancement strategies.

6) On-treatment monitoring visits: 10 cotinine monitoring visits will occur over 12 weeks. Monitoring visits will begin 1 week after the quit date and occur weekly through week 8, followed by every other week through week 12. These visits serve 2 purposes: a) to assess self-reported smoking behavior, varenicline use and side effects, and selected other measures (section VI.A), and b) to objectively verify smoking status through measurement of saliva cotinine. Cotinine is the major metabolite of nicotine, and saliva cotinine is widely used to verify smoking abstinence in research settings because it can be measured reliably, rapidly, inexpensively, and with minimal invasiveness using saliva collection devices and cotinine detection kits at the point of care.[28] These qualities make the measurement of saliva cotinine a useful tool for verifying smoking abstinence in contingency management setting since contingent rewards are most effective when delivered immediately.[59, 60] Frequent objective verification of smoking status provides frequent opportunities for abstinence-contingent financial rewards for incentive arm participants and serves as an attention control for control arm participants.

Point-of-care saliva cotinine testing will be conducted using commercially available, professional-grade kits with documented performance characteristics and a cut-off level of 30 ng/ml. Current examples include the Alere iScreen OFD cotinine oral fluid screening device and the Jant Accutest Saliva Cotinine Test, although other tests with similar performance characteristics may be used depending upon availability and supply chain considerations. Instructions and procedures provided by the manufacturer will be carefully followed during collection. Collected saliva samples will be discarded immediately upon reading the results and will be handled as if they were potential biohazards. No identifying information will be affixed to the samples. For participants in the financial incentives arm, payments will be based exclusively on having a negative point-of-care saliva cotinine test and will not rely on self-report.[30] Payments for negative cotinine levels will begin at $25 and increase by $5 for each successive abstinent measurement up to a maximum of $70. Non-abstinent measurements, or failure to provide a saliva sample for cotinine measurement, will result in no payment and will reset the subsequent payment for an abstinent test back to the starting value of $25. An exception to this reset procedure will be made for participants who miss a monitoring visit due to COVID-related

isolation or quarantine requirements (described in section G). These individuals will not have their incentive payment schedule reset to the starting value for a COVID-related absence, but rather will resume payments at the value following where they left off prior to the isolation/quarantine period. A similar exception will be made if the saliva cotinine test produces an invalid result. If this occurs during an intervention arm monitoring visit, the participant will be offered the chance to repeat the test for a 2nd and 3rd time on the same day and up to 3 times on the next business day. If invalid results persist on repeat testing, or if a participant refuses to attempt repeat testing, they will not be paid for the monitoring visit, but their incentive payment will not reset to the starting value and will remain at the value where they left off during their previous monitoring visit.

To facilitate equivalent levels of contact for the incentive and control arm conditions, control arm participants will also have the opportunity to undergo cotinine monitoring visits according to the same schedule used for incentive arm participants. Control arm participants will receive a fixed amount of $10 for completing each monitoring visit, irrespective of their saliva cotinine levels**.** If a control arm participant has an invalid saliva cotinine test result, they will be offered the opportunity to repeat the test up to two more times during that visit, but they will still be paid $10 for attending the monitoring visit and attempting to complete at least one saliva test even if no valid results are produced. In addition to verifying abstinence through the above point-of-care measurements, we will also formally assess the primary study outcome at the week 12 monitoring visit. This will involve collecting a second saliva sample for send-out cotinine testing at a contracted laboratory that provides a more precise quantitative result using a chemiluminescence immunoassay or gas chromatography/mass spectrometry.[61] We currently plan for J2 Laboratories to conduct this testing, although other laboratories offering assays with equivalent performance characteristics may be engaged if circumstances dictate doing so. For these tests, participants will be asked to hold a saliva collection sponge in their mouths for about 5 minutes. When the sponge is completely wet, it will be placed back into the collection tube. The tube will be sealed and labeled with the participant's study ID number so that no personal information is associated with the saliva sample. Instructions and procedures provided by the contracted laboratory will be carefully followed during collection. Samples will be batch mailed to the contracted laboratory, where saliva cotinine levels will be quantified. Sample results will be reported to research staff via password protected email exchange.

During the week 12 visit, we will also administer a follow-up survey to reassess several of the baseline data variables (listed below in section VI.A). Participants who miss their 12-week monitoring visit will be able to complete the outcome cotinine saliva test and follow-up survey within 2 weeks.

7) Post-treatment outcome assessment visit: A post-treatment visit will occur at 24 weeks. The purpose of this visit is to assess and verify smoking abstinence following the removal of all study treatments. Abstinence testing at this timepoint will be similar to the strategy outlined above for assessing on-treatment abstinence at week 12. Smoking abstinence will be assessed for all participants using the quantitative laboratory saliva cotinine test. In addition, smoking abstinence will be assessed by the point-of-care saliva cotinine test to allow staff to immediately categorize participants for potential qualitative interviews as described below. We will also administer a follow-up survey to reassess several of the baseline variables (listed below in section VI.A.) at each of these post-treatment assessment visits. Participants who miss their 24-week outcome testing visit will be able to complete the outcome cotinine saliva tests and follow-up surveys within 2 weeks of this timepoint.

8) Qualitative interviews: We will conduct qualitative interviews with a purposively-selected sample of incentive arm participants to better understand why, how, and under what circumstances they A) achieve (or not) abstinence in response to financial incentives and B) maintain (or not) abstinence after incentives are stopped. Information gathered during these interviews will help generate hypotheses about potential mechanisms for on-treatment and post-treatment effects and inform future modifications of the intervention.

To address part A of this aim, we will purposively sample incentive arm participants at 12 weeks according to their on-treatment abstinence profile, categorized as follows:

1) Non-responders (N=10): Earned <5 abstinence-contingent reward payments and divided into 2 subgroups a) concordant reporters (N=5): showed concordance between self-reported and biochemically-verified abstinence and b) non-concordant reporters (N=5): showed non-concordance between self-reported and biochemically-verified abstinence throughout the trial.
2) Partial responders (N=10): Earned ≥5 abstinence-contingent reward payments but was non-abstinent at the 12-week outcome assessment.
3) Responders (N=10): earned ≥5 abstinence-contingent reward payments and was abstinent at the 12-week outcome assessment.

Abstinence at the 12-week outcome assessment will be based on participant's point-of-care saliva cotinine level. To account for a potential treatment effect of these interviews[44] on subsequent 24-week smoking outcomes, we will interview 30 control arm participants at 12 weeks about their general experience with attempting to quit smoking in the setting of homelessness. To attempt to achieve balance on abstinence profile, we will aim to recruit 20 control arm participants who were non-abstinent at 12 weeks and 10 who were abstinent at 12 weeks based on point-of-care salivary cotinine testing.

To address part B of this aim, at 24 weeks we will purposively sample from 2 strata of incentive arm participants who achieved abstinent cotinine levels at 12 weeks:

1) Sustained responders (N=10): Abstinent cotinine levels at 12 and 24 weeks
2) Non-sustained responders (N=10): Abstinent cotinine level at 12 weeks but not at 24 weeks.

Abstinent cotinine levels will be determined by a negative laboratory saliva cotinine result at 12 weeks and a negative point-of-care saliva test at 24 weeks. The point-of-care cotinine test will be used at the 24-week timepoint to ensure that interviews can be scheduled and completed within 2 weeks (since it may take up to 30 days for the laboratory cotinine test result to return).

Actual sample sizes for each response profile may be adjusted until thematic saturation is reached. This sampling approach will ensure a diverse set of experiences with the financial incentives intervention and will aid in understanding the factors underpinning variability in treatment responsiveness. Part A participants will be recruited by study staff within 2 weeks of their 12-week follow-up visit. Part B participants will be recruited by study staff within 2 weeks of their 24-week follow-up visit. Audiotaped interviews lasting up to 60 minutes will be conducted by trained study staff following semi-structured interview guides addressing the content areas described below in section VI.A. Participants will receive $30 in remuneration on their study-issued debit card for participating in these interviews.

B. Drugs

Participants in both study arms will be offered a prescription for varenicline, an FDA-approved, first-line smoking cessation medication[33] that has been shown to be safe and effective in at-risk populations, including those with comorbid psychiatric conditions,[38] alcohol use disorder [39] and substance use disorders.[40, 41] In general, varenicline prescriptions will be issued by the study clinician who will meet with participants at the randomization visit to assess their health history and relevant comorbid conditions. In most cases, participants will receive a 1-month prescription for varenicline from the study clinician according to the recommended 7-day loading procedure of 0.5 mg daily on days 1-3 then 0.5 mg twice daily on days 4-7 before reaching the target dose of 1 mg twice daily on day 8.[52]

After the completion of the enrollment visit, study staff will contact the participant's PCP to inform them of their patient's enrollment in a stop smoking study in which varenicline will be offered. Unless the participant reports a history of specific comorbidities, PCP permission will not be required before the study clinician meets with the participant and prescribes varenicline at the typical dosage. However, PCPs will be invited to respond to study staff messages to express any questions or concerns, and if the PCP recommends that varenicline is not prescribed, the study clinician will follow this recommendation. For participants with selected comorbidities, including seizure history, chronic kidney disease, or higher-risk mental states, we will follow a systematic algorithm to ensure safe varenicline prescribing (Appendix 2). Comorbidities will be assessed in various ways, including a) participants' responses to the eligibility screener and baseline survey items related to chronic medical conditions and mental health symptoms, b) review of documented comorbidities within participants' EHR, and c) baseline clinical assessment by the study clinician. The action plans in response to specific comorbidities (as visualized in Appendix 2) are explained further below:

1) **Seizures:** During the baseline survey, participants will be asked if they have a lifetime history of seizures, and if yes, whether they had a seizure in the past year. If the participant has had a seizure within the past year, study staff will send the participant's PCP a direct message via Epic on the same day as the enrollment visit informing them of their patient's enrollment in the study and requesting input from the PCP regarding whether a prescription for varenicline is appropriate. The study clinician will not prescribe varenicline to such a participant until explicit permission from the PCP is granted. If the participant has not had a seizure within the past year, study staff will still send the participant's PCP a direct message informing them of their patient's enrollment in the study and invite their input if they have any questions or concerns; however, the clinician will proceed with prescribing varenicline unless the PCP directly expresses that the participant should not take varenicline.
2) **Chronic kidney disease (CKD):** For participants with a history of CKD, our varenicline prescribing protocols are based on past research on varenicline use in patients with renal impairments and the recommendations listed on the Pfizer varenicline packet insert**.**[52, 62] During the baseline survey, participants will be asked if they have a lifetime history of CKD, and if yes, whether they are currently on dialysis. For participants on dialysis, the clinician will prescribe varenicline at a maximum dose of 0.5 mg once daily (a quarter of the typical maximum dose). For participants who are not on dialysis, the clinician will recommend that the participant completes lab testing to ascertain current serum eGFR levels. If the participant refuses new labs, the clinician will prescribe

varenicline at a maximum dose of 0.5 mg twice per day (half the maximum typical dose), which is the recommended dose for patients with severe renal impairment (eGFR < 30). Participants who agree to have labs drawn will be prescribed varenicline according to their eGFR results. If the participant's eGFR is <30, the clinician will prescribe varenicline at a maximum dose of 0.5 mg twice per day. If the participant's eGFR is ≥30, the clinician will up-titrate varenicline to the typical maximum dose of 1.0 mg twice per day. In all cases, study staff will send an Epic message to the PCPs of participants with any degree of CKD to inform them of their patient's enrollment in the study; however, the clinician will proceed with prescribing varenicline according to the above well-defined clinical protocols unless the PCP directly recommends otherwise.

3) **Higher-risk mental health states:** Participant suicidality will be assessed during the eligibility screener, and other mental health symptoms will be assessed during the baseline survey using multiple assessments, as described in section VI.A. If the participant reports vague suicidal ideation but is otherwise found to be at low risk of suicide based on the C-SSRS primary care screening instrument (patients with high risk will be excluded) or if the participant is considered moderate risk of suicide only due to suicidal behavior over 12 months ago, study staff will send the participant's PCP a direct message via Epic on the same day as the enrollment/baseline survey study visit informing them of their patient's enrollment in the study and requesting input regarding whether prescribing varenicline is appropriate. The same procedure will occur for participants with high scores on standardized mental health symptom instruments administered during the baseline survey (see Appendix 2). The study clinician will not prescribe varenicline to the patient until explicit permission from the PCP is granted.

At the time of the baseline clinician visit, the participant may be undecided on whether they want to try varenicline, or final approval from the participant's PCP or other provider may still be pending. In these instances, the clinician can delay issuing a varenicline prescription for up to 2 weeks. Undecided participants will be told to inform study staff if they decide to take varenicline. If PCP/provider approval is still pending, the study clinician will directly contact the PCP/provider to ensure that a direct answer is provided within the 2-week window. Upon meeting with the participant, the study clinician may determine based on chart review or clinical assessment that the participant has concerning comorbidities, symptoms, or circumstances that were not uncovered during screening and enrollment. In these cases, the clinician may determine that direct PCP input is necessary before prescribing varenicline and will direct message the participant's PCP to obtain this input before prescribing.

For participants who are prescribed varenicline at baseline, treatment will continue for 12 weeks, distributed in 1-month allotments in conjunction with follow-up clinician visits at 3 and 7 weeks to assess medication adherence and tolerance. Dose adjustments will be made for participants who experience non-serious side effects.

The clinician will electronically send varenicline prescriptions directly to the BHCHP pharmacy or to an alternative pharmacy (based on patient request and current supply), where participants will be instructed to fill their prescriptions. The majority of participants will have MassHealth insurance and can obtain their prescription with a $3.40 copay that can be waived by the pharmacy if needed. The BHCHP pharmacy is also a covered entity under the 340B low-cost medication program and can therefore dispense varenicline at a very low cost (~$0.55 per month) to participants without insurance. Given the low cost of varenicline under 340B pricing

and the low likelihood of recruiting participants without MassHealth, BHCHP has agreed to voucher the medication costs for participants who have no insurance or who have insurance that only offers varenicline at a high copay. If a participant requests to use an alternative pharmacy, the clinician will electronically send the varenicline prescription to this preferred pharmacy instead.

C. Devices

Participants who do not have a mobile phone of their own will be given a low-cost mobile device (~$30/unit) with a 12-month talk and text plan (~$125/year through Tracfone) to facilitate communication and follow-up. If a participant loses or sells their device, the phone will not be replaced, and their plan will be deactivated. To incentivize phone retention, participants who still have their device at the end of the study will be allowed to keep it.

D. Procedures

There will be no procedures or surgical interventions in this study.

E. Data Collection

All data will be collected using password-protected, Mass General Brigham-approved laptops or tablets with full-disk encryption. We will use the Mass General Brigham-hosted Research Electronic Data Capture (REDCap) application for data collection and management. The specific data elements collected at each study visit are detailed below in section VI.

F. Electronic Communication

The Twilio text messaging feature will be integrated into our REDCap database. This will allow study staff to send participants automated text message reminders about their next scheduled appointment and the maximum potential payment they can earn at this visit. Text messages will not include any identifying information and participants can opt out at any time by texting the word “STOP” (see Appendix 1 for sample text messages). Participants must consent to receive these text messages. The consent form includes information outlined in the Mass General Brigham guidelines for texting research subjects.[63]

Study staff may use Mass General Brigham’s HIPAA-compliant video conference platforms, Microsoft Teams or Enterprise Zoom, to administer surveys and complete coaching sessions as part of the team’s in-person remote COVID-19 safety protocol (see section V.A). Participants who prefer this form of engagement will arrive to the BHCHP clinic where on-site study staff will set up a Teams or Zoom call on a study tablet for the participant to use. Participants will participate in the video call using headphones in a private or semi-private space within the clinic; study staff will administer the survey or complete the coaching session via Teams or Zoom either on-site (in a separate room) or remotely. This will minimize in-person contact between study staff and participants while allowing participants and study staff to engage in potentially sensitive conversations during the surveys and coaching sessions. For safety and security, no Teams or Zoom links will be shared with participants. Teams or Zoom meetings will require passwords and will not be shared with anyone other than study staff. Participants will be instructed not to use the chat function during these meetings as the feature is not encrypted. Participants will also be advised that photographs and recordings of Teams or Zoom calls are not allowed.

Participants may meet with the study clinician via MGB-hosted Microsoft Teams, MGB Enterprise Zoom, or BHCHP's Epic/OCHIN integrated HIPAA-compliant Zoom platform. The third option allows participants to engage with the clinician in the manner currently used to provide COVID-safe virtual clinical care at BHCHP.

Study staff may also engage with participants over the phone. If participants prefer remote virtual study visits for COVID-19 precautions, study staff will conduct surveys, coaching visits, interviews, and some clinician visits over the phone. Study staff will call participants from study cellphones or BHCHP land lines. Participants will provide a contact number during the enrollment visit and can update the contact number as necessary.

Study staff may use Imprivata cortex, a HIPAA-compliant secure communications platform, to communicate with the study clinician using designated work iPhones encrypted with iOS MobileIron Mobile Device Management (MDM) software.

G. COVID-19 Contingency Plans:

The team is engaged in contingency planning and will continue to monitor hospital, state, and federal guidance on COVID-19. Should a resurgence of COVID interfere with the ability to implement the study protocol as written here, the team will implement contingency plans that will be adopted for the circumstances and restrictions present at the time of a future surge.

Participants and staff will be asked to follow current CDC guidelines regarding isolation and/or quarantine in the event of developing COVID-19 symptoms or experiencing a significant COVID-19 exposure. The implications of COVID-related absences for incentive arm payments are discussed above.

H. Procedures for Restarting Enrolled Participants

As described in protocol amendment 11, all study activities were paused on 07/06/21 due to a global shortage of varenicline resulting from elevated levels of nitrosamine contaminants prompting a recall of all Pfizer-manufactured varenicline on the market. The safety considerations related to this are addressed in section VII.B. At the time of study suspension, 11 participants were enrolled.

Once the study resumes, the 11 participants who were previously enrolled will be approached by phone or in person to be invited to restart the study. Participants interested in restarting the study will do so under their original study ID number and randomized group assignment but will be asked to redo all other study activities. If participants are interested in restarting the study, they will be asked to complete the eligibility screener questions and saliva test (see section V.A.1.) to confirm their continued eligibility before completing two study restart appointments as described below.

To ease the response burden, participants will be offered the option to complete the eligibility screener questions over the phone. If their responses to the questions suggest that they are still eligible to participate, they will be invited to meet with study staff in person at JYP within two weeks to confirm their eligibility with a saliva test for cotinine. If the cotinine saliva test is consistent with current smoking, participants will immediately proceed with the first study restart appointment. Participants who opt to complete all components of the eligibility re-screening in person will meet with study staff at JYP and, if still eligible, will be invited to complete the first study restart appointment either immediately or within 2 weeks. Participants who are found to no

longer be eligible during any component of the eligibility re-screening process will be given the option to either screen again at a later date (if the reason for ineligibility is a time-limited issue such as connectedness to care) or to unenroll from the study.

At the first study restart appointment, participants will follow procedures similar to the enrollment appointment discussed in section V.A.2. Study staff will review an updated version of the consent form with participants, and participants will be required to sign this updated version of the consent form to continue study participation. Study staff will then confirm participants' current demographic and contact information and repeat the full baseline survey. Participants will receive $25 for completing this first appointment. Following this first appointment, all PCPs will be messaged using the same procedures described in sections V.A.4 and V.B. PCPs will need to give permission for the study clinician to prescribe varenicline for participants who report various health concerns during their most recently-completed eligibility screener and baseline survey.

The second study restart appointment must be completed within 4 weeks of the first study restart appointment. Participants will follow the same procedures described in sections V.A.3 and V.A.4, with the exception that participants who were previously randomized will retain their original treatment group assignment. Participants who do not have their own phone will be offered a study phone and will be paid $10 for completing this study visit.

Participants who complete both the first and second appointments will restart the study at week 0, which corresponds with the quit date and first tobacco coaching session, approximately 1 week after their second study restart appointment.

All data collected during the original study launch prior to the pause will be exported from REDCap and archived in the secure Lab Archives system to allow for a clear audit trail of any changes to the data. In REDCap, new instances of forms will be created for any repeatable forms, and new data will overwrite old data as needed for non-repeatable forms. Study staff will log all instances of updates to existing non-repeatable forms within REDCap. The most recent data will be used for analyses and earlier data will be disregarded.

VI. BIOSTATISTICAL ANALYSIS

A. Specific data variables

The specific data elements collected at each visit are as follows:

1) Screening visit data elements: This visit will focus on assessing variables related to the inclusion and exclusion criteria. Variables collected during this visit will include:

- First and last name
- Date of birth
- Native language and self-reported comfort communicating in English among non-native speakers
- Ever smoked ≥100 cigarettes
- Current cigarettes per day
- Saliva cotinine level ≥30 ng/mL, based on point-of-care testing
- Prior serious allergic reactions to varenicline

- Currently pregnant, planning to become pregnant, or breastfeeding
- Readiness to try quitting smoking within the next 3 months
- Prior experience with homelessness
- Presence of BHCHP electronic health record
- Name of BHCHP PCP (and if PCP has been seen within the past year)
- History of psychiatric hospitalization within the past 3 months
- Suicidal ideation and behavior, based on the C-SSRS[48]
- Among individuals who are eligible and wish to schedule an enrollment visit or who are ineligible but would be interested in attempting screening again in the future, we will collect their current phone number (if any) to facilitate communication about the enrollment visit

2) Enrollment visit data elements: When individuals present for enrollment, we will confirm that they have previously screened eligible for the study. For those who wish to enroll in the study, we will collect additional demographic and contact information:

- Gender
- Pronouns
- Social security number
- Current residence or place where sleeping at night
- Current phone number (if any); confirm/update number if previously collected at screening visit
- Emergency contact information
- BHCHP medical record number
- Insurance coverage listed within BHCHP electronic health record

We will also conduct a baseline survey assessing the following variables at the time of enrollment: Italicized measures will be collected during follow-up surveys at weeks 12 and 24:

Domains	Measures
Sociodemographic	Race/ethnicity; education; health insurance (all based on items from the 2003 HCH User Survey[23, 64] and our prior survey work[45, 65, 66])
Homelessness	*Homelessness* episodes and duration[67]; *living situation*; *past-month subsistence difficulties*[53]
Mental/physical health	*General health status (SF-1)*[68, 69]; *single item measurement of cigarette craving*[70]*;* chronic medical conditions; Domains related to COVID-19, including diagnosis and symptom history[71, 72], change in quitting motivation [73, 74], and receipt of the COVID-19 vaccine; *AUDIT* [76-78]*; DAST-10* [78,79]*; past 3-month drug use inventory*[80,81] ; *PHQ-9* [82,83]*; GAD-7*[84]; MDQ[85, 88, 89]; PSQ[92, 95, 96]
Tobacco use	Age of initiation; *past quit attempts (≥24 hours)*; use of cessation aids; use of e-cigarettes or vape products*; cigarettes/day;* Fagerstrom Test for Nicotine Dependence[88]; *10-point importance and confidence scales*[2, 16, 18]; *stage of change*[91, 92]; *Contemplation Ladder*[91]; social support for quitting[18], past month use of alternative tobacco products [66]

3) On-treatment monitoring visit data elements: The following variables will be collected at the timepoints specified in parentheses. If participants miss their week 12 monitoring visit, the underlined elements will be asked during the follow-up survey visit up to 2 weeks later.

- Point-of-care saliva cotinine level (every monitoring visit, per Figure 3)
- Date and time last smoked all or most of a cigarette (every monitoring visit)
- Date and time of last puff of cigarette (every monitoring visit)
- Number of smoking days in the past 7 days (every monitoring visit)
- Average number of cigarettes per day (every monitoring visit)
- Use of vape or e-cigarette in past 7 days (every monitoring visit)
- Use of other tobacco products in past 7 days (every monitoring visit)
- Single item measurement on cigarette craving (every monitoring visit)[70]
- Past week use of varenicline prescribed by study clinician (every monitoring visit)
- Average number of varenicline pills taken per day (if applicable, based on whether the participant is prescribed varenicline by the study clinician; every monitoring visit)
- Use of other quit smoking aids (every monitoring visit)
- Side effects to varenicline, including abnormal dreams, aggressive/erratic behavior, headaches, nausea, sleep disturbance/insomnia, vomiting, and other (if applicable; every monitoring visit)
- Suicidal thoughts, intention, and behaviors since last study visit, as measured by a modified version of the C-SSRS (if applicable; every monitoring visit).[48]
- Other adverse events not related to varenicline if reported by participant (every monitoring visit)
- All items italicized in the baseline survey table above at 12 weeks, or within 2 weeks post
- Saliva cotinine level from results of laboratory cotinine testing at 12 weeks, or within 2 weeks post

4) Post-treatment outcome assessment visit data elements: The following variables will be collected at 24 weeks, or within 2 weeks post, unless otherwise specified in parenthesis.

- Point-of-care saliva cotinine level (incentive participants only)
- Date and time last smoked all or most of a cigarette
- Date and time of last puff of a cigarette
- Number of smoking days in the past 7 days
- Number of quit attempts in the past 3 months
- Use of cessation aids
- Use of vape or e-cigarette in the past 7 days
- Use of other tobacco products in the past 7 days
- All items italicized in the baseline survey table above
- Laboratory saliva cotinine level

5) Coaching session data elements: Baseline, 2, 4, 8, and 12 weeks (or within 1 week)

- Confidence to quit smoking (or to stay quit)
- Importance of quitting smoking (or staying quit)
- Past-month quit attempts
- Summary of coaching session, including experiences delivering the intervention including the ease of delivery (including the length, scheduled time); the apparent acceptability and relevance; comprehension of the material by the participants; and factors that impeded or assisted in the delivery, and any issues related to safety or potential harms that emerge.

6) Qualitative interview data elements: 12 and 24 weeks (or within 2 weeks post)

We will create 2 interview guides for incentive arm participants selected for qualitative interviews: one guide to address part A of this aim at 12 weeks, and a second guide to address part B of this aim at 24 weeks. Both will be structured around exploring the cognitive ('why?'), procedural ('how?'), and contextual ('under what circumstances?') dimensions of participants' response (or lack of) to the financial incentives intervention during and after treatment.

▪ ***Cognitive:*** Questions in this domain will explore *why* participants abstain (or not) from smoking in response to financial incentives. **A)** At 12 weeks, interviewers will probe: the perceived impact of incentives on smoking cognitions, such as readiness, motivation, and confidence to quit or importance of quitting; the extent to which the extrinsic motivation of incentives was internalized by participants; the importance of incentive dollar amounts, frequency, and format on the perceived potency of incentives; the perceived fairness and understandability of the incentives scheme; and the overall utility of financial incentives in promoting cessation, particularly in relation to other treatments tried by participants. **B)** At 24 weeks, interviewers will probe: how participants coped with transitioning off incentives; how smoking cognitions, such as readiness, motivation, and confidence to quit or importance of quitting, changed following the removal of incentives; and the extent to which participants were successful (or not) in shifting from extrinsic to intrinsic motivational pathways.

▪ ***Procedural:*** Questions in this domain will explore *how* participants abstain (or not) from smoking in response to financial incentives. **A)** At 12 weeks, interviewers will probe: participants' use of varenicline and other pharmacotherapies, coaching or other counseling services, or other mainstream or alternative strategies for quitting; how these supplemental strategies facilitated or impeded their response to the incentives intervention; and whether the intervention had spillover effects in promoting related healthy behaviors that reinforced abstinence, such as increasing physical activity or reducing concurrent substance use. **B)** At 24 weeks, the above areas will be explored again, but with a focus on assessing whether these behavioral strategies for sustaining abstinence increased, waned, or remained stable after incentives were removed.

▪ ***Contextual:*** Questions in this domain will explore the individual and social *circumstances* under which participants abstain (or not) from smoking in response to financial incentives. At both 12 and 24 weeks, interviewers will probe the ways in which *individual material circumstances*, such as housing status, food security, personal safety, and other basic survival needs; *individual comorbidities*, such as physical ailments, psychiatric symptoms, and concurrent substance use disorders; and *social milieu characteristics*, such as friends who smoke, second-hand smoke exposure, social support for quitting, and access to smoke-free settings, collectively influence **A)** on-treatment abstinence initiation and **B)** post-treatment abstinence maintenance in response to the financial incentives intervention. We will also probe whether and how this relatively 'high-touch' intervention strategy fits within the broader social context of participants' lives in order to optimize the approach for subsequent studies aiming to disseminate and implement this treatment modality.

A third interview guide will be developed for control arm participants that will generically explore their experiences with quitting smoking in the context of homelessness or unstable housing.

<u>B. Study Endpoints</u>

1) Primary outcome: The Aim 1A outcome is saliva cotinine-verified 7-day smoking abstinence at 12 weeks. Participants who report not smoking in the past 7 days and have a saliva cotinine level of <10 ng/mL at the week 12 timepoint will be considered abstinent.

2) Secondary outcome: The Aim 1B outcome is 7-day smoking abstinence at 24 weeks, based on self-report and verified by a salivary cotinine level of <10 ng/mL.

3) Other outcomes: Other outcomes include 7-day smoking abstinence at weeks 1-11 (defined as no smoking the past 7 days and having a point-of-care saliva cotinine level <30 ng/ml), use of varenicline or other smoking cessation medications (assessed by self-report and BHCHP chart review), use of other tobacco treatment resources, changes in past-month drug and alcohol use and psychiatric symptoms (assessed with the AUDIT [76-78], DAST-10 [78,79],drug use inventory, PHQ-9, [82,83] GAD-7,[84] at 12 and 24 weeks).

C. Statistical Methods

Quantitative analysis: Quantitative analysis will be based on the intention-to-treat principle. We will use Chi-squared tests to assess the difference between arms on attainment of the primary and secondary outcomes. Cochran-Mantel-Haenszel tests will determine whether the intervention effect is homogenous across study sites. We will use logistic regression to assess the intervention effect while adjusting for site. In primary analysis, participants who do not provide a saliva sample or are lost to follow-up will be assumed non-abstinent. A sensitivity analysis will use multiple imputation to impute missing outcomes data based on non-missing variables.[94, 95] In addition to cross-sectional analyses of the primary and secondary outcomes, we will conduct a repeated measures analysis of smoking status at 12 and 24 weeks to assess the overall impact of financial incentives on smoking abstinence. This analysis, which provides greater statistical power than cross-sectional analyses, will use generalized estimating equations (GEE) to account for the correlated data structure. We will also use GEE to analyze the other outcomes of changes in cigarette consumption, WHO ASSIST drug and alcohol scores, and mental health scores, each measured at baseline and 12 and 24 weeks.

Qualitative analysis: All interviews will be transcribed verbatim by a professional service and analyzed using NVivo 11 software. Data analysis will be based on a grounded theory approach[94] and will occur concurrently with data collection to ascertain when thematic saturation is reached for each sampling stratum. Two trained study staff members, working in parallel under the direction of Drs. Baggett, Park, and Kruse, will begin by open-coding the raw transcript data to form initial categories using a principally inductive approach.[95] During weekly team meetings, the method of constant comparison[96,97] will be used to iteratively refine these categories, to resolve discrepancies through discussion and reference to raw data until high inter-rater reliability (K≥0.80) is achieved, and to organize emergent major and minor themes into a hierarchical framework. Analyses will compare findings across treatment response profiles to generate insights about the reasons for response variability. Consistent with the embedded-experiment mixed methods design,[44] the qualitative data will be used to answer the basic question: “To what extent do the qualitative process findings enhance the understanding of the experimental outcomes?”[98] Toward that end, the qualitative findings will be included in the main paper reporting the RCT results to provide a more nuanced picture of why and how the intervention produced the outcomes it did. Subsequent papers will make further use of the qualitative data to examine why certain subgroups fare better with financial incentives, to introduce a conceptual framework for incentive-based health interventions for homeless

individuals, to share lessons learned about the practicalities of designing and deploying an incentives intervention for this population, and to inform future modifications of the intervention.

D. Power Analysis

Our power calculation is based on the Aim 1A outcome of cotinine-verified smoking abstinence at 12 weeks. With a sample arm of 90 per arm, we will have >80% power to detect a difference in abstinence at 12 weeks of 4% in the control arm and 17.5% in the incentives arm at a two-tailed p of 0.05.

VII. RISKS AND DISCOMFORTS

The potential risks and discomforts associated with this study are detailed below. The methods for mitigating these risks and monitoring the safety of participants are described in section IX.B.

A. Complications of surgical/non-surgical procedures

Not applicable.

B. Drug side effects and toxicities

Participants will be offered a prescription for varenicline. Common side effects of varenicline are nausea, sleep problems, constipation, gas, and vomiting. Other possible, but less common, side effects include cardiovascular (chest pain, hypertension, tachycardia), sleep walking, allergic reactions, or serious skin reactions. Participants who are taking varenicline prescribed by the study clinician will be assessed for varenicline side effects and suicidality at each on-treatment monitoring visit. Procedures for addressing participants with significant side effects and suicidality are described below (section IX. D.).

In June 2021, Pfizer announced a halt in global distribution of varenicline (brand name: Chantix) and a voluntary recall of selected lots after finding heightened levels of N-nitroso-varenicline (a nitrosamine compound) in some pills. Although the risk posed by N-nitroso-varenicline is uncertain, nitrosamine compounds in general are considered carcinogenic when exposure occurs in sufficient doses over prolonged periods of time. The nitrosamine levels found in Pfizer's varenicline product exceeded the FDA's acceptable intake limit of 37 ng per day. In September 2021, Pfizer extended its recall to all lots of varenicline.

The FDA has since approved two generic versions of varenicline: one manufactured by Apotex and one manufactured by Par Pharmaceuticals. The FDA also announced that they would not object to manufacturers distributing varenicline tablets above the FDA's original acceptable intake limit of 37 ng per day but below an interim acceptable intake limit of 185 ng per day. Both of the above generic versions of varenicline distributed by Apotex and Par have levels of N-nitroso-varenicline that are within the FDA's interim acceptable intake limit.[99]

Study staff are working closely with the BHCHP pharmacy to ensure participants receive a varenicline product that falls within these interim safe limits. During informed consent, staff will inform participants of the risk of contamination of varenicline products while also clarifying that the versions they will receive have been deemed safe by the FDA.

C. Device complications

Not applicable.

D. Psychosocial (non-medical) risks

i) Psychological and/or physical discomfort: Quitting smoking can be psychologically stressful and, at times, physically uncomfortable because of cravings and nicotine withdrawal symptoms, such as irritability, depressed mood, sleep difficulty, and concentration difficulty. Participants will be asked to what extent they have craved cigarettes at each on-treatment monitoring visit.

ii) Risk to privacy: We will collect and record identifying information (e.g. name, date of birth, and social security number) and ask participants about potentially sensitive topics. There is a risk to privacy if this data is compromised.

E. Radiation risks

Not applicable.

G. Potential loss of study mobile phone

Participants may be at minimal risk of a breach of privacy if someone else gains access to their phone during the study. Therefore, we will inform participants of this risk during recruitment and encourage participants to mitigate this risk by 1) not sharing their phone with others, 2) password protecting their mobile device, and 3) in the event of loss, notifying research staff to terminate service to the device. Automated appointment reminder text messages will be sent to participants. These text messages are designed to convey relevant information to participants while having a protective level of ambiguity.

VIII. POTENTIAL BENEFITS

A. Potential benefits to participating individuals

Potential benefits for participants include the opportunity to receive assistance with smoking cessation, which may reduce their risk of tobacco-related health complications in addition to reducing the amount of money they direct toward purchasing cigarettes. The scope and magnitude of these potential benefits outweigh the risks to human subjects.

B. Potential benefits to society

As in the general population, cigarette smoking is a major contributor to morbidity and mortality among homeless people.[14, 15] Strategies to reduce smoking among homeless people may reduce the personal and financial costs of smoking-related health complications in this population. Knowledge gained from this study could contribute to this effort by improving the treatment of homeless smokers in other settings.

IX. MONITORING AND QUALITY ASSURANCE

We judge the proposed study to represent a low-risk phase III behavioral intervention trial. In view of the vulnerable nature of the study population, we will create a Data and Safety Monitoring Board (DSMB), consisting of researchers not involved in the study who have expertise in clinical trials and/or vulnerable populations, to oversee the integrity of the data and

the safety of participants. The objectives and procedures of the DSMB are explained further below (section IX.I.). The following data and safety monitoring procedures (sections IX.A.-IX.G.) will be implemented throughout the study.

A. Data acquisition and monitoring

All data will be collected using password-protected, Mass General Brigham-approved laptops or tablets with full-disk encryption. We will use the Mass General Brigham-hosted Research Electronic Data Capture (REDCap) application for data collection and management. REDCap is a secure, HIPAA-compliant web-based application hosted by Mass General Brigham HealthCare Research Computing Enterprise Research Infrastructure & Services (ERIS). Because a Mass General Brigham username is required for logging in to REDCap, all activity on study documents is electronically logged and therefore traceable. To help guard against errant data entries, REDCap has built-in functions providing real-time data entry validation to help ensure accuracy and completeness. Data will be collected according to a standardized protocol that will detail which data elements should be collected at each study visit and the methods for doing so. We will operationalize this protocol by using the calendar function in REDCap to specify which data collection forms to administer on which dates for each participant. Each data collection form will have instructions or prompts for collecting the required data elements, and the response fields for each item will have appropriate ranges and formats to ensure that the data is entered in a valid way.

Data collected in REDCap is saved by default to a secure, HIPAA-compliant server. To help ensure the safety and integrity of the study data, the data will be periodically exported from REDCap and backed up to a HIPAA-secure shared file area (SFA) accessible only to authorized study staff after logging on to the Mass General Brigham network. Data saved to the study SFA can be accessed only via the Mass General Brigham-approved computing device, which by default includes antivirus software and, if the device is portable, full-disk encryption. The SFA is backed up nightly by the Mass General Brigham Information Systems department to guard against data loss or corruption. Access to the study SFA will be overseen by the PI and can be changed only by a designated key-giver (who is independent of the study) under the explicit direction of the PI. In addition to the SFA, selected data elements may also be stored on a project-dedicated Mass General Brigham Microsoft SharePoint site. Data saved on the project-dedicated SharePoint site will be accessible only to study staff.

The qualitative interviews conducted at 12 and 24 weeks will be recorded by a microphone connected directly to a password-protected, Mass General Brigham-approved laptop or tablet with full-disk encryption. Audio files will be backed up to the PI's SFA described above and then deleted from the portal device.

The study data will be examined on a weekly basis by the REDCap database programmer, working in conjunction with the PI, to identify patterns of missing data or non-response, to ensure that critical variables are being captured and recorded as intended, and to generate recruitment and enrollment reports for review by the PI in conjunction with the co-investigators. Free-text notes recorded by data collectors will be examined to identify potentially problematic items that may require additional clarification. The database programmer will prepare cleaned, de-identified analytic datafiles for use by the biostatistician to conduct the data analyses described in the Research Strategy. Analyses will occur periodically throughout the study and

the findings will be reported in annual progress reports to the NIH and in continuing review reports for the Mass General Brigham IRB.

B. Quality assurance

The tobacco coach will complete a checklist indicating topics covered during the counseling sessions and will record process notes after each session. He/she will record experiences delivering the intervention including the ease of delivery (including the length, scheduled time); the apparent acceptability and relevance; comprehension of the material by the participants; and factors that impeded or assisted in the delivery, and any issues related to safety or potential harms that emerge.

Using a random selection process, the tobacco coach will identify a sub-sample of 15% of sessions to audio record. A clinical psychologist will periodically review the recordings and provide direct feedback to the tobacco coach using a standard coaching evaluation form rating adherence to the protocol, adherence to motivational interviewing principles, use of motivational interviewing tools/techniques, and participant engagement. The coach will obtain verbal consent from participants before starting the recording. Sessions will be recorded by a microphone connected directly to a password-protected, Mass General Brigham-approved laptop or tablet with full-disk encryption. Audio files will be backed up to the PI's SFA described above and deleted from the portable device. Audio files will also be destroyed immediately after review. The coaching evaluation forms will not contain any identifying information and will be securely stored on Microsoft Sharepoint.

C. Safety Monitoring

The eligibility criteria for the study are designed to identify individuals who would most likely benefit from the proposed intervention. These criteria represent an expansion of the criteria used in our pilot RCT,[27] enabling the proposed intervention to reach a broader target population. Although all current smokers should be advised to stop smoking and offered assistance in quitting, we believe that the proposed financial incentives approach is best targeted to individuals who are least contemplative about quitting (i.e. planning to quit in the next 3 months). Whether financial incentives might motivate interest in smoking cessation among pre-contemplative smokers is a separate scientific question that merits separate investigation.

During eligibility screening, participants will be asked about potential contraindications to varenicline, including questions about suicidality via the primary care screening version of the C-SSRS (see Appendix 3).[48] Individuals at low risk of suicide will be allowed to participate while being made aware of available behavioral health care resources, including 24-hour crisis line numbers and on-site mental health services at BHCHP. Individuals at moderate risk of suicide only due to history of suicidal behavior >12 months prior (and not due to current suicidal thoughts) will be allowed to participate if all other criteria are met, and will be made aware of available behavioral health care resources. Individuals at moderate risk of suicide due to history of suicidal behavior in the past 3-12 months (and not due to current suicidal thoughts) will be excluded and made aware of available behavioral health care resources. Individuals at moderate risk of suicide due to suicidal thoughts with methods but without intent will be excluded from the study, provided 24-hour crisis line numbers, and encouraged to make an appointment with a behavioral health clinician (at BHCHP or elsewhere) within 3 business days.

Individuals at high risk of suicide due to past 3-month suicidal behavior (with no current suicidal intent) will also be excluded from the study and encouraged to make an appointment with a behavioral health clinician within 3 business days. Individuals at high risk of suicide due to current suicidal intent based on the C-SSRS will be excluded from the study and referred immediately for an urgent on-site same-day mental health evaluation by BHCHP clinical staff.

To ensure that eligible participants have an adequate understanding of the potential risks associated with study participation, all participants will be informed of these risks in plain language on a written informed consent document that will be read aloud to each participant, making no assumption of literacy. Participants will be informed of the option of not participating in the study and that their decision regarding study participation will in no way impact their ability to receive future services at BHCHP. Following a practice we established in our prior survey work involving homeless smokers[45, 66, 101] and further refined in our pilot RCT for homeless smokers,[27] we will confirm individuals' understanding of the consent materials with basic knowledge questions about the consent document content to ensure that they have the capacity to provide informed consent. Individuals who can correctly answer these questions will be asked to sign the paper consent form if they wish to enroll in the trial. A signed copy will be retained by study staff and a second signed copy of the consent form will be given to participants for their own records.

During the trial, participants will be asked proactively about side effects at regular intervals during monitoring visits and encouraged to report side effects to varenicline at any time. Adverse reactions will be tracked and addressed according to the adverse event procedures outlined below. Participants will be asked to rate the severity of their side effects as none, mild, moderate, or severe. Mild reactions will be recorded and monitored, and participants will be encouraged to let study staff know if they worsen or persist. If a participant rates a side effect as moderate, study staff will ask if the participant wants to speak with a clinician. If so, the clinician will phone participants within 48 hours to assess their symptom(s) and formulate a plan, which could include continuing as is, modifying the dose of varenicline, or stopping varenicline. If a participant experiences severe side effects, study staff will advise the participant to immediately stop taking varenicline. The study clinician and PI will be notified and will follow-up with the participant within 24 hours to decide with the participant about whether to remain off varenicline or resume the medication at a lower dose. Severe, potentially life-threatening reactions (e.g., cardiac complications) will prompt immediate on-site medical assessment by a health care provider at BHCHP headquarters or at a nearby hospital. The study clinician and PI will be notified and will follow-up with the participant within 24 hours.

Study staff will also proactively assess suicidality at every on-treatment monitoring visit using a modified version of the C-SSRS (see Appendix 3).[48] Participants at low risk for suicide based on the C-SSRS will be made aware of available behavioral health care resources, including crisis line numbers and on-site mental health services at BHCHP. Participants at moderate risk for suicide based on the C-SSRS will be given 24-hour crisis line numbers and encouraged to schedule a visit with their PCP or an on-site behavioral health provider within 2 business days, with assistance from study staff. The study clinician or PI will call these participants within 24 hours to discuss their suicidality and reinforce the above evaluation plan. Participants at high risk for suicide based on the C-SSRS will be escorted immediately to the on-site BHCHP clinic for an urgent mental health evaluation by BHCHP clinical staff. Study staff will advise these participants to stop varenicline. The study clinician and PI will be notified and will follow-up with

the participant within 24 hours to discuss the plan for moving forward. In instances in which participants show moderate or high risk of suicide based on the C-SSRS, study staff will communicate with participants' PCPs via secure Epic messaging regarding the outcome of this assessment within 2 business days (if moderate risk) or within 24 hours (if high risk). Although suicidality will not be proactively assessed during tobacco coaching sessions, if participants spontaneously bring up suicidal thoughts, the tobacco coach will follow similar procedures to the monitoring visits and assess suicidality risk using the modified C-SSRS and react accordingly based on level of risk.

If a participant misses their monitoring visit, this will trigger an automated text message to their study phone or personal phone advising them to call study staff if they are experiencing any side effects or other concerns related to their participation in the study (see Appendix 1).

If a participant calls study staff with concerns, study staff will make a note of any reported side effects and their severity in a manner similar to that which would occur during an in-person monitoring visit. However, to improve the efficiency of phone encounters, reduce the use of participants' cell phone minutes and allow the participant to direct the conversation in a more fluid way, a complete checklist of side effects and the C-SSRS scale will not be administered by default during these phone calls unless dictated by participants' reported symptoms. If a participant reports mental health concerns, this will prompt administration of the (C-SSRS) over the phone, with triage according to the algorithm outlined for in-person monitoring visits.

Psychological status (including depression and anxiety symptoms) will be formally assessed at baseline, and at 12 and 24 weeks, providing additional opportunities to identify and address any psychological discomforts that participants may be experiencing. If any participant screens positive for any mental health disorders listed, study staff will ask participants whether they are currently receiving behavioral health care and assist them with connecting or reconnecting with such care, either at BHCHP or at an outside facility (if preferred by the participant).

Study staff will be trained to recognize the signs of an intoxicated participant and to activate a response plan appropriate to the level of symptoms or impairment. Participants demonstrating evidence of mild substance intoxication will be informed of on-site behavioral health services to address substance use. Participants with more profound levels of intoxication causing substantial impairment in functioning and well-being will be referred for immediate on-site medical evaluation. The clinic at BHCHP headquarters has walk-in medical and behavioral health appointments available every weekday to support the on-site referrals describe above.

D. Confidentiality safeguards:

All participants will receive an identification number that will be used for all forms, interviews, transcripts, and intervention materials. Forms and databases with identifying information include the demographics form and the paper consent form. The demographics form will be completed in REDCap. Consent forms will be scanned into REDCap as part of each participant's individual study record. The physical consent form will be stored in a locked filing cabinet at BHCHP that only study staff can access. Study staff will periodically hand-carry the consent forms in a locked box from the BHCHP site to the main MGH office where the files will be permanently stored in a locked filing cabinet.

Identifiable information from participants who are approached and screened but not enrolled will be saved with participant permission until recruitment ends. Once recruitment ends, we will remove any identifying information from all non-enrolled participants from our REDCap database as well as from any log sheets for tracking recruitment efforts. Identifiers in the REDCap database will be erased by using the REDCap data import tool to overwrite all identifying information. Identifiers within any additional log sheets for tracking recruitment will be manually erased. Identifiable data will be replaced with non-identifiable placeholder data.

All staff who come into contact with Human Subjects and/or data collected from Human Subjects will have received prior training about confidentiality during the course of their IRB-required Human Subjects training, which is conducted using the Collaborative IRB Training Initiative (CITI) system.

E. Outcomes Monitoring

Outcome monitoring will occur on a rolling basis each time a participant provides a saliva cotinine sample. Because of the low-risk nature of the study, we will not conduct a formal interim analysis of the data or define rules for early stopping of the trial.

F. Adverse Events

1) Assessing Events: As described in section VI.A., we will assess for adverse events at every study visit. For participants who are prescribed varenicline through the study clinician, this will include queries about potential side effects to varenicline using a standardized checklist in addition to the C-SSRS for suicide risk assessment weekly through week 8 and every other week through week 12.

Participants will also be reminded to report problems, whether related or potentially related to study participation or not, to study personnel between scheduled intervention visits and assessments. They will be instructed on how to contact study personnel should problems occur during intervals between visits. Adverse events will be documented, carefully assessed to determine expectedness, relatedness, and potential for harm, and steps will be taken to prevent future similar events from occurring. Violations of participant privacy/confidentiality will be treated as an unanticipated problem related to the study and will be considered reportable.

2) Reporting of reportable events to the IRB: We will adhere to the Mass General Brigham policy statement on “Reporting Unanticipated Problems including Adverse Events.” Consistent with this policy, an adverse event will be defined as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.” A serious adverse event will be defined as an adverse event that results in death, is life-threatening, requires hospitalization, causes persistent or significant disability, or requires medical or surgical intervention. The PI and his designated study staff will be responsible for the monitoring of adverse events in study participants.

Adverse events reported to the PI or other study staff will be documented in an adverse event report containing a description of the event, the date and time of onset, the date and time of resolution, the expectedness of the event, the relationship to the study, the seriousness of the event, and the action taken in response to the event. An adverse event will be deemed

unexpected if the nature, severity, or frequency of the event is not consistent with a known or foreseeable risk given the research procedures, the characteristics of the subject population, or with an expected progression of an underlying condition. The following attribution scale will be used to describe the relationship of the adverse event to the study protocol: unrelated, possibly related, or related to the protocol.

Unexpected adverse events that are at least possibly related to the research and suggest the research puts participants at increased harm will be reported to the Mass General Brigham IRB and Data and Safety Monitoring Board (DSMB; see section H below) within 5 working days or 7 calendar days. Serious adverse events that are unexpected and at least possibly related to the research will be assumed to suggest that the research puts participants at increased risk of harm and will be reported to the Mass General Brigham IRB and DSMB within the same time frame. Any action resulting in a temporary or permanent suspension of this study will be reported to the NIH funding agency's program official. A summary safety report detailing all adverse events and their handling will be included in annual study progress reports to the Mass General Brigham IRB (if requested) and the NIH funding agency. Adverse event reports and annual safety summaries will be documented by study ID number; personal identifiers will not be included in these reports.

3) Reporting mechanisms to NCI and DSMB: The PI will report reportable events to the NCI Project Officer by phone or email within 5 working days and follow-up with a written report (by fax or email) within 10 calendar days, detailing any additional information and whether or not the event is related to participation in the study or may affect future participation in the study.

The PI will make a report to the Chairperson of the DSMB within 5 working days of learning of the event. The DSMB will review the event (usually on the phone or via email) and make a report via email to the PI, who will forward the report to the IRB and NCI Project Officer.

G. Protocol Adherence

1) Research staff: The study coordinators will be trained on the data collection protocols described above. Their understanding of these protocols will be assessed by asking them to demonstrate competency in using the REDCap data collection forms and in collecting the saliva samples for both point-of-care and laboratory cotinine testing.

2) Tobacco coach: The tobacco coach will receive online and in-person training to prepare for the role. S/he will first complete the online 9-module course on "Basic Skills for Working with Smokers" sponsored by the University of Massachusetts Center for Tobacco Treatment Research & Training (UMass TTRT).[101] The tobacco coach will then attend a Tobacco Treatment Specialist Core Certificate training (UMass TTRT).[102] Prior to the start of the study, the tobacco coach will be required to demonstrate competency in fulfilling the duties of the role. The tobacco coach will not be a certified Tobacco Treatment Specialist (TTS) because this is a lengthy and intensive process that would reduce the generalizability of the intervention to more resource-limited homeless health care settings that do not currently have a TTS and count not afford to hire or train one. This approach is consistent with the concept of "task-shifting" endorsed by the World Health Organization for delivering needed care in resource-limited settings.[103]

H. Data and Safety Monitoring Board (DSMB)

The DSMB will provide independent oversight of the safety monitoring of study participants. The DSMB will review the study protocol and recommend changes that may improve the protocol, as needed. Throughout the duration of the study, the DSMB will revisit the protocol to identify any emerging issues and recommend improvements and will monitor the safety of study participants by assessing social impact and adverse event reports. The DSMB may recommend modifications to the protocol, or early termination of the study, should overwhelmingly significant benefits or risks become apparent, or if the DSMB deems that the trial cannot be completed successfully.

The main objectives of the DSMB include:

i. ***Protocol review***: The DSMB will review the study protocol and data and safety monitoring plan before data collection begins. The DSMB will recommend modifications to the study protocol and safety monitoring plan as needed. The members will also review subsequent protocol changes proposed by the investigators and will recommend a timeframe for implementing protocol changes. The NCI Program Officer will be informed of any protocol changes recommended by the DSMB.
ii. ***Participant safety***: The DSMB will review unanticipated problems, adverse events, and other reportable events and formulate recommendations to continue, amend, or terminate the study based on established safety criteria.
iii. ***Study progress:*** The DSMB will review screening, recruitment, and retention data to ensure that the study can be completed in a reasonable timeframe to be of significant clinical relevance.

1) Frequency of DSMB meetings: The DSMB will review and provide input on study procedures prior to the start of enrollment. Following the start of enrollment, the DSMB will convene at designated intervals to provide oversight of study progress and safety**.** The first oversight meeting will occur 6 months following the start of enrollment. Subsequent oversight meetings will occur annually, or more frequently if deemed necessary by the DSMB Chair or the study PI. Potential formats for DSMB oversight and review of study procedures could include phone conferences, video conferences, or carefully documented email exchanges at the discretion of the DSMB chair, DSMB members, and the PI Dr. Travis Baggett.

2) DSMB reports: The DSMB Chair will prepare a draft report of the DSMB review. The report will outline and summarize all discussions during the meeting and will clearly note recommendations and action items from the Board. The report will be reviewed by all members of the DSMB and the Principal Investigator prior to finalizing the report. The DSMB Report will be forwarded to the Project Officer. Clerical support will be provided by the MGH site as requested by the Chair of the DSMB. Following each DSMB review, the Chair shall prepare a written report to be finalized within 14 working days following the formal meeting and be sent to the PI. The report will review the 2 main aspects of the trial for which the DSMB is responsible as noted in section 2 above (see sections I.I & I.II). In addition, following each study review, the DSMB will recommend one of the following:

i. Continuation of the trial using the current protocol and statistical plan.
ii. Continuation of the project with modifications as outlined by the Board.
iii. Immediate suspension of the trial for safety reasons for all participants, with a recommended plan of follow-up to minimize subject harm (requires unanimous vote).
iv. Suspension of enrollment but continuation of assigned treatments for already-enrolled participants. Enrollment may resume once clarifications requested by the Board have been addressed and resolved (requires unanimous vote).

3) Discussion of confidential material: No communications, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided by written policy. Study data are strictly confidential and must not be divulged to any nonmember of the Board except as indicated by policy.

4) Disclosure of any conflict of interest: DSMB members will have no financial and/or scientific ties to the outcome of the study. Each DSMB member will be asked to provide financial disclosure documentation prior to the start of the member's term. Each DSMB member will also be asked to sign a confidentiality statement promising not to disclose any data.

X. PARTICIPANT REMUNERATION

The remuneration of homeless individuals for participating in research studies requires special consideration of both practical and ethical issues. This section contains a discussion of these issues.

A. Summary of remuneration plan

All participants will receive $25 for completing a baseline survey at the enrollment visit, $10 for the randomization and clinician visit, and $15 for every tobacco coaching session they attend. Additionally, all participants will receive $30 for completing follow-up data collection visits (survey and laboratory saliva cotinine test) at 12 and 24 weeks. Up to 80 selected participants (50 from the incentives arm, 30 from the control arm) will each receive $30 for completing a qualitative interview. Participants will also be offered token items (e.g fidget toys, tote bags, single serve snacks or drinks) at study visits to help pass time while completing the saliva assessments. Prior focus group data revealed that such items are greatly appreciated in this population and may enhance study visit adherence.

Participants in the incentive arm will get escalating payments for negative cotinine levels based on the point-of-care saliva test. Participants will receive payments starting at $25 and increasing by $5 for each successive cotinine-negative measurement, up to a maximum of $70. Non-negative measurements, or failure to provide a saliva sample for cotinine testing, will result in no payment and will reset the subsequent payment back to the starting value of $25 (exceptions to this procedure are described above in section V.A). The maximum cotinine-based reward payout will be $475. Thus, the maximum total amount that participants in the incentives arm can earn over the course of the study will be $675: $25 for the baseline survey, $10 for the randomization visit, $75 if they attend all tobacco coaching sessions, $60 if they attend both follow-up data collection visits, $475 for cotinine-based abstinence at all visits, and $30 if they complete a qualitative interview. However, our pilot RCT experience suggests that actual remuneration will average out to about 41% of the maximum, or about $277 per incentive arm participant.

Participants in the control arm will get fixed $10 payments for attending on-treatment monitoring visits regardless of their cotinine levels on the point-of-care saliva test. The maximum total amount that participants in the control arm can earn over the course of the study will be $300: $25 for the baseline survey, $10 for the randomization visit, $75 if they attend all tobacco coaching sessions, $100 if they attend all on-treatment monitoring visits, $60 for completing both follow-up data collection visits, and $30 if they complete a qualitative interview.

All payments will be issued to participants via reloadable Visa debit cards through a secure payment portal hosted by CT Payer. CT Payer is a secure web-based platform that facilitates HIPAA-compliant clinical trial and study-related payments onto reloadable Visa cards. Unlike payment systems offered by banks and third-party payment providers, CT Payer does not collect any protected health information from research participants. Study staff members add funds onto cards through an online payment portal, reimbursing participants accordingly following study visits. Funds are available to the study participant immediately and may be used with the same convenience as a debit card. Every card is shipped with a "Card Kit" containing the number of CT Payer's 24/7 customer service line, which can be called for card balance inquiries or to report a lost/stolen card. All payments are tracked in real-time and may be organized by date, participant ID, or card number. On-demand reporting features provide a convenient way to determine the total amount a participant received in reimbursements for tax or other purposes. Participants will sign a form acknowledging receipt when they receive a new CT Payer Visa debit card. **As demonstrated in the email communication attached to this application, the Mass General Brigham Research Controller, Rhonda Lowe, has reviewed and approved our proposed use of CT Payer for this study.**

If the CT Payer platform is temporarily unable to load payments onto existing debit cards or issue new cards, we will provide participants with single-use, non-reloadable gift cards in denominations of $10, $15, $25, and $30 to correspond to the payment amount they are entitled to receive for each visit completed. Participants will sign a form acknowledging receipt when they receive a non-reloadable gift card. Participants who complete visits over the phone may choose to pick up their non-reloadable gift card in person or have it mailed to them. **This alternative payment system was also reviewed by Rhonda Lowe who agreed that this was in accordance with MGB policy.**

B. Potential for misuse

It is possible that some participants will choose to use their debit card or gift cards to purchase cigarettes, alcohol, or other items that are potentially harmful to their health. This possibility is not unique to homeless people and does not justify violating the ethical principle of remunerating homeless participants in a fashion that is equitable with non-homeless people. Furthermore, the use of debit cards or gift cards (rather than cash) for study payments markedly limits their ability to be used for the purchase of illicit drugs. Another safeguard is that participants in the incentives arm receive payments only for biochemically-verified smoking abstinence. If a participant chooses to apply this payment toward alcohol, drugs, or tobacco, then it is highly likely that the participant will relapse with smoking and/or miss the following study visit, resulting in no payment at that visit and resetting the subsequent reward payment to the starting value. In this fashion, the contingency management framework provides a negative feedback loop for curtailing payments if a participant's substance use worsens. In support of this notion, we observed no worsening of alcohol or drug use severity, measured serially using the Addiction Severity Index,[105-108] among participants in our pilot RCT. Indeed, in qualitative exit interviews, many participants reported using their debit cards to purchase food, clothing, and personal care items they otherwise would not have been able to afford.

C. Consideration of undue influence

Undue influence occurs when the monetary value of remuneration for research participation is so great in relation to the context of an individual's life circumstances that his/her decision about

whether to participate is inappropriately overwhelmed in favor of participating because of the financial reward for doing so.[108] Below we consider the use of undue influence by study arm, since the participant payment scheme differs for each arm. Importantly, we note that the concept of "coercion" does not apply to either study arm, because there is no threat of negative consequences for non-participation in the study or for not quitting smoking while in the study.[108] As per the informed consent procedures outlined below, participants will be informed in plain language that their decision about whether to participate in the study will have no adverse impact on their ability to receive care at any BHCHP site.

Control arm: The compensation provided to individuals in the control arm is consistent with that provided to homeless participants in other clinical trials[110] and appropriate to the level of effort being asked of participants in this arm; therefore, payments made to control arm participants do not constitute undue influence.

Incentives arm: Compared with control arm participants, participants in the incentives arm have the potential to earn greater total compensation, raising the issue of whether this higher dollar amount may represent undue influence. However, we do not believe that the proposed payments for incentive arm participants constitute undue influence for several reasons. First, the incentives are not designed to encourage trial participation per se and are not guaranteed by simply agreeing to participate. Rather, they are tied specifically to biochemically-verified smoking abstinence, a health behavior for which there is substantial evidence of benefit,[110,111] unanimous professional consensus,[113-116] and minimal risk of harm. Second, the financial rewards for smoking abstinence do not require participants to accept a level of risk they would not ordinarily accept in the absence of incentive payments. Indeed, we are targeting individuals who report a goal of quitting smoking within the next 3 months, and the incentives are designed to help facilitate that goal. Third, the incentive payments proposed in this study are comparable to those used in our pilot RCT in Boston, in a pilot study of contingent financial rewards for homeless smokers in Dallas,[29] and in a financial incentive study involving smokers with schizophrenia,[116] while being less than those used in a financial incentive trial for low-income smokers in Switzerland.[118, 119] For these reasons, we deem the financial rewards for smoking abstinence offered to participants in the incentives arm to be scientifically and ethically appropriate and consistent with the evidence base in this area.

D. Participant safety

In the setting of homelessness, carrying or possessing items with a high dollar value potentially poses a risk that the person carrying such an item could be targeted for theft. During 2 focus groups with homeless smokers that we conducted in planning for our pilot RCT, participants reported satisfaction with the proposed debit card format and stated that they would not feel unsafe carrying them. This sentiment was subsequently echoed by participants in our pilot RCT. This is due in large part to the fact that the monetary balance on a given debit card is not readily apparent, diminishing its street value and improving the sense of safety that participants have when carrying it on themselves.

E. Exemption from Mass General Brigham remuneration policy

As noted above, the Mass General Brigham Research Controller has granted an exemption from the Mass General Brigham policies on "Payments to Human Subjects for Participation in Research" and "Cash Control and Accountability for Payments to Human Subjects for Participation in Research" and has approved our proposed use of CT Payer to manage

participant remuneration via reloadable Visa debit cards in the manner described above (see attached email communication).

XI. REFERENCES

1. Baggett TP, Rigotti NA. Cigarette smoking and advice to quit in a national sample of homeless adults. *American Journal of Preventive Medicine*. Aug 2010;39(2):164-72. doi:S0749-3797(10)00322-3 [pii]

10.1016/j.amepre.2010.03.024
2. Connor SE, Cook RL, Herbert MI, Neal SM, Williams JT. Smoking cessation in a homeless population: there is a will, but is there a way? *Journal of General Internal Medicine*. May 2002;17(5):369-72. doi:jgi10630 [pii]
3. Snyder LD, Eisner MD. Obstructive lung disease among the urban homeless. *Chest*. May 2004;125(5):1719-25.
4. Szerlip MI, Szerlip HM. Identification of cardiovascular risk factors in homeless adults. *Am J Med Sci*. Nov 2002;324(5):243-6.
5. Tsai J, Rosenheck RA. Smoking Among Chronically Homeless Adults: Prevalence and Correlates. *Psychiatr Serv*. Apr 1 2012;63(6):569-76. doi:10.1176/appi.ps.201100398
6. Chau S, Chin M, Chang J, et al. Cancer risk behaviors and screening rates among homeless adults in Los Angeles County. *Cancer Epidemiol Biomarkers Prev*. May 2002;11(5):431-8.
7. Jamal A, Agaku IT, O'Connor E, King BA, Kenemer JB, Neff L. Current cigarette smoking among adults--United States, 2005-2013. *MMWR Morb Mortal Wkly Rep*. Nov 28 2014;63(47):1108-12. doi:mm6347a4 [pii]
8. Hwang SW, Orav EJ, O'Connell JJ, Lebow JM, Brennan TA. Causes of death in homeless adults in Boston. *Ann Intern Med*. Apr 15 1997;126(8):625-8.
9. Morrison DS. Homelessness as an independent risk factor for mortality: results from a retrospective cohort study. *Int J Epidemiol*. Jun 2009;38(3):877-83. doi:dyp160 [pii]

10.1093/ije/dyp160
10. Hwang SW, Wilkins R, Tjepkema M, O'Campo PJ, Dunn JR. Mortality among residents of shelters, rooming houses, and hotels in Canada: 11 year follow-up study. *BMJ*. 2009;339:b4036.
11. Hibbs JR, Benner L, Klugman L, et al. Mortality in a cohort of homeless adults in Philadelphia. *N Engl J Med*. Aug 4 1994;331(5):304-9.
12. Baggett TP, Hwang SW, O'Connell JJ, et al. Mortality among homeless adults in Boston: shifts in causes of death over a 15-year period. *JAMA Intern Med*. Feb 11 2013;173(3):189-95. doi:1556797 [pii]

10.1001/jamainternmed.2013.1604
13. Hwang SW. Mortality among men using homeless shelters in Toronto, Ontario. *JAMA*. Apr 26 2000;283(16):2152-7. doi:jcu90010 [pii]
14. Baggett TP, Chang Y, Porneala BC, Bharel M, Singer DE, Rigotti NA. Disparities in Cancer Incidence, Stage, and Mortality at Boston Health Care for the Homeless Program. *Am J Prev Med*. Nov 2015;49(5):694-702. doi:S0749-3797(15)00161-0 [pii]

10.1016/j.amepre.2015.03.038
15. Baggett TP, Chang Y, Singer DE, et al. Tobacco-, alcohol-, and drug-attributable deaths and their contribution to mortality disparities in a cohort of homeless adults in Boston. *Am J Public Health*. Jun 2015;105(6):1189-97. doi:10.2105/AJPH.2014.302248
16. Butler J, Okuyemi KS, Jean S, Nazir N, Ahluwalia JS, Resnicow K. Smoking characteristics of a homeless population. *Subst Abus*. Dec 2002;23(4):223-31. doi:453647 [pii]

17. Okuyemi KS, Caldwell AR, Thomas JL, et al. Homelessness and smoking cessation: insights from focus groups. *Nicotine & Tobacco Research*. Apr 2006;8(2):287-96. doi:V468461608327310 [pii]

10.1080/14622200500494971
18. Arnsten JH, Reid K, Bierer M, Rigotti N. Smoking behavior and interest in quitting among homeless smokers. *Addictive Behaviors*. Aug 2004;29(6):1155-61. DOI: 10.1016/j.addbeh.2004.03.010. doi:10.1016/j.addbeh.2004.03.010

S0306460304000851 [pii]
19. Baggett TP, Lebrun-Harris LA, Rigotti NA. Homelessness, cigarette smoking and desire to quit: results from a US national study. *Addiction*. Nov 2013;108(11):2009-18. doi:10.1111/add.12292
20. Cigarette smoking among adults--United States, 2003. *MMWR Morb Mortal Wkly Rep*. May 27 2005;54(20):509-13. doi:mm5420a3 [pii]
21. Baggett TP, Tobey ML, Rigotti NA. Tobacco use among homeless people--addressing the neglected addiction. *N Engl J Med*. Jul 18 2013;369(3):201-4. doi:10.1056/NEJMp1301935
22. Businelle MS, Cuate EL, Kesh A, Poonawalla IB, Kendzor DE. Comparing homeless smokers to economically disadvantaged domiciled smokers. *Am J Public Health*. Dec 2013;103 Suppl 2:S218-20. doi:10.2105/AJPH.2013.301336
23. Baggett TP, O'Connell JJ, Singer DE, Rigotti NA. The unmet health care needs of homeless adults: a national study. *Am J Public Health*. Jul 2010;100(7):1326-33. doi:AJPH.2009.180109 [pii]

10.2105/AJPH.2009.180109
24. Burling TA, Burling AS, Latini D. A controlled smoking cessation trial for substance-dependent inpatients. *J Consult Clin Psychol*. Apr 2001;69(2):295-304.
25. Okuyemi KS, Thomas JL, Hall S, et al. Smoking cessation in homeless populations: a pilot clinical trial. *Nicotine Tob Res*. Oct 2006;8(5):689-99. doi:N62771P24387P631 [pii]

10.1080/14622200600789841
26. Okuyemi KS, Goldade K, Whembolua GL, et al. Smoking characteristics and comorbidities in the power to quit randomized clinical trial for homeless smokers. *Nicotine Tob Res*. Jan 2013;15:22-8. doi:10.1093/ntr/nts030

10.1093/ntr/nts030. Epub 2012 May 15.
27. Baggett TP, Chang Y, Yaqubi A, McGlave C, Higgins ST, Rigotti NA. Financial incentives for smoking abstinence in homeless smokers: A pilot randomized controlled trial. *Nicotine Tob Res*. Aug 18 2017;doi:10.1093/ntr/ntx178
28. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res*. May 2002;4(2):149-59. doi:10.1080/14622200210123581
29. Businelle MS, Kendzor DE, Kesh A, et al. Small financial incentives increase smoking cessation in homeless smokers: a pilot study. *Addict Behav*. Mar 2014;39(3):717-20. doi:S0306-4603(13)00409-7 [pii]

10.1016/j.addbeh.2013.11.017
30. Carpenter VL, Hertzberg JS, Kirby AC, et al. Multicomponent smoking cessation treatment including mobile contingency management in homeless veterans. *J Clin Psychiatry*. Jul 2015;76(7):959-64. doi:10.4088/JCP.14m09053
31. Gayman C, Anderson K, Pietras C. Saliva cotinine as a measure of smoking abstinence in contingency management–A feasibility study. *The Psychological Record*. 2017;67(2):261-272.

32. Jarvis MJ, Russell M, Benowitz NL, Feyerabend C. Elimination of cotinine from body fluids: implications for noninvasive measurement of tobacco smoke exposure. *American journal of public health*. 1988;78(6):696-698.
33. Fiore MC, Jaén CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. *Rockville, MD: US Department of Health and Human Services*. 2008;
34. Leone FT, Zhang Y, Evers-Casey S, et al. Initiating Pharmacologic Treatment in Tobacco-Dependent Adults. An Official American Thoracic Society Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*. 2020;202(2):e5-e31.
35. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *Jama*. 2006;296(1):56-63.
36. Davies NM, Taylor AE, Taylor GM, et al. Varenicline versus nicotine replacement therapy for long-term smoking cessation: an observational study using the Clinical Practice Research Datalink. *Health Technology Assessment (Winchester, England)*. 2020;24(9):1.
37. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane database of systematic reviews*. 2016;(5)
38. Raich A, Ballbè M, Nieva G, et al. Safety of varenicline for smoking cessation in psychiatric and addicts patients. *Substance Use & Misuse*. 2016;51(5):649-657.
39. Hurt RT, Ebbert JO, Croghan IT, Schroeder DR, Hurt RD, Hays JT. Varenicline for tobacco-dependence treatment in alcohol-dependent smokers: A randomized controlled trial. *Drug and alcohol dependence*. 2018;184:12-17.
40. Rohsenow DJ, Tidey JW, Martin RA, et al. Varenicline versus nicotine patch with brief advice for smokers with substance use disorders with or without depression: effects on smoking, substance use and depressive symptoms. *Addiction*. 2017;112(10):1808-1820.
41. Raich A, Pinet C, Ballbè M, et al. Multimodal treatment for smoking cessation with varenicline in alcoholic, methadone-maintained, and psychotic patients: A one-year follow-up. *Tobacco induced diseases*. 2018;16
42. Shelley D, Cantrell J, Wong S, Warn D. Smoking cessation among sheltered homeless: a pilot. *American journal of health behavior*. 2010;34(5):544-552.
43. O'Connell JJ, Oppenheimer SC, Judge CM, et al. The Boston Health Care for the Homeless Program: a public health framework. *Am J Public Health*. Aug 2010;100(8):1400-8. doi:AJPH.2009.173609 [pii]

10.2105/AJPH.2009.173609
44. Creswell JW, Plano Clark VL. Chapter 3: Choosing a Mixed Methods Design. *Designing and Conducting Mixed Methods Research*. 2nd ed. Sage; 2011:53-106.
45. Baggett TP, Rigotti NA, Campbell EG. Cost of Smoking among Homeless Adults. *N Engl J Med*. Feb 18 2016;374(7):697-8. doi:10.1056/NEJMc1508556
46. Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews*. 2015;(12)
47. Richardson J, Stephens S, Yates L, et al. Pregnancy outcomes after maternal varenicline use; analysis of surveillance data collected by the European Network of Teratology Information Services. *Reproductive Toxicology*. 2017;67:26-34.
48. Posner K BD, Lucas C, Gould M, Stanley B, Brown G, et al. Columbia-suicide severity rating scale (C-SSRS). Screener with triage for primary health settings. 2008.
49. Anthenelli RM, Benowitz NL, West R, et al. 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. *The Lancet*. 2016;387(10037):2507-2520.

50. Ashare RL, Thompson M, Serrano K, et al. Placebo-controlled randomized clinical trial testing the efficacy and safety of varenicline for smokers with HIV. *Drug and alcohol dependence*. 2019;200:26-33.
51. Pachas GN, Cather C, Pratt SI, et al. Varenicline for smoking cessation in schizophrenia: safety and effectiveness in a 12-week open-label trial. *Journal of dual diagnosis*. 2012;8(2):117-125.
52. *CHANTIX - Highlights of Prescribing Information*. Medication Insert. 2019. 2/2019.
53. Gelberg L, Gallagher TC, Andersen RM, Koegel P. Competing priorities as a barrier to medical care among homeless adults in Los Angeles. *Am J Public Health*. Feb 1997;87(2):217-20.
54. Baggett TP, Rigotti NA, Chang Y, Campbell EG. Subsistence difficulties and their association with perceived barriers to quitting smoking among homeless smokers in Boston. presented at: Scientific abstract presented at the 2016 Annual Meeting of the Society of General Internal Medicine; May 13, 2016 Hollywood, FL.
55. Koegel P, Burnam MA, Farr RK. Subsistence Adaptation Among Homeless Adults in the Inner City of Los Angeles. *Journal of Social Issues*. 1990;46(4):83-107.
56. Baggett TP, Singer DE, Rao SR, O'Connell JJ, Bharel M, Rigotti NA. Food insufficiency and health services utilization in a national sample of homeless adults. *J Gen Intern Med*. Jun 2011;26(6):627-34. doi:10.1007/s11606-011-1638-4
57. Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. . Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; May 2008.
58. American Lung Association. Freedom from Smoking Online. Accessed March 30, 2016.
59. Higgins ST, Redner R, White TJ. Contingency Management and the Community Reinforcement Approach. In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. *The ASAM Principles of Addiction Medicine*. 5th ed. Wolters Kluwer; 2014:877-893:chap 58.
60. Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. *Addiction*. Feb 2006;101(2):192-203. doi:ADD1311 [pii]

10.1111/j.1360-0443.2006.01311.x
61. Ballesteros J. Cotinine Testing. In: Sporn N, editor. 2020.
62. Faessel HM, Obach RS, Rollema H, Ravva P, Williams KE, Burstein AH. A review of the clinical pharmacokinetics and pharmacodynamics of varenicline for smoking cessation. *Clinical pharmacokinetics*. 2010;49(12):799-816.
63. *Texting Patients and Research Subjects: Guidelines for Obtaining Consent*. 2020.
64. Greene J, Fahrney K, Byron M. Health Care for the Homeless User/Visit Surveys, RTI Project Number 07147.021. . Research Triangle Park, NC: RTI International; 2004.
65. Baggett TP, Campbell EG, Chang Y, Magid LM, Rigotti NA. Posttraumatic Stress Symptoms and Their Association With Smoking Outcome Expectancies Among Homeless Smokers in Boston. *Nicotine Tob Res*. Oct 27 2015;doi:ntv238 [pii]

10.1093/ntr/ntv238
66. Baggett TP, Campbell EG, Chang Y, Rigotti NA. Other tobacco product and electronic cigarette use among homeless cigarette smokers. *Addict Behav*. Apr 19 2016;60:124-130. doi:S0306-4603(16)30146-0 [pii]

10.1016/j.addbeh.2016.04.006
67. Burt MR, Aron LY, Douglas T, et al. Homelessness: Programs and the People They Serve: Findings of the National Survey of Homeless Assistance Providers and Clients: Technical Report. Washington, D.C.: U.S. Department of Housing and Urban Development, Office of Policy Development and Research; 1999.

68. DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P. Mortality prediction with a single general self-rated health question. A meta-analysis. *J Gen Intern Med*. Mar 2006;21(3):267-75. doi:JGI291 [pii]

10.1111/j.1525-1497.2005.00291.x
69. Larson CO. Use of the SF-12 instrument for measuring the health of homeless persons. *Health Serv Res*. Jun 2002;37(3):733-50.
70. West R, Ussher M. Is the ten-item Questionnaire of Smoking Urges (QSU-brief) more sensitive to abstinence than shorter craving measures? *Psychopharmacology*. 2010/02/01 2010;208(3):427-432. doi:10.1007/s00213-009-1742-x
71. Oelsner. MESA COVID-19 Questionnaire. 1.0 ed. The Multi-Ethnic Study of Atherosclerosis (MESA) Website: Collaborative Health Studies Coordinating Center; 2020.
72. Symptoms of Coronavirus. Centers for Disease Control and Prevention. Updated 5/13/2020. Accessed 10/1/2020, 2020.
73. Kowitt SD, Cornacchione Ross J, Jarman KL, et al. Tobacco Quit Intentions and Behaviors among Cigar Smokers in the United States in Response to COVID-19. *Int J Environ Res Public Health*. Jul 25 2020;17(15)doi:10.3390/ijerph17155368
74. Release of Optional COVID-19 Questions for the MDS. North American Quitline Consortium 10/14/2020, 2020.
75. Saunders JB, Aasland OG, Organization WH. *WHO Collaborative Project on the Identification and Treatment of Persons with Harmful Alcohol Consumption. Report on phase I: the development of a screening instrument*. 1987.
76. Bohn MJ, Babor TF, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. *Journal of studies on alcohol*. 1995;56(4):423-432.
77. Doran KM, Rahai N, McCormack RP, et al. Substance use and homelessness among emergency department patients. *Drug and alcohol dependence*. 2018;188:328-333.
78. Skinner HA. The drug abuse screening test. *Addictive behaviors*. 1982;7(4):363-371.
79. Yudko E, Lozhkina O, Fouts A. A comprehensive review of the psychometric properties of the Drug Abuse Screening Test. *Journal of substance abuse treatment*. 2007;32(2):189-198.
80. Humeniuk R, Ali R, Babor TF, et al. Validation of the alcohol, smoking and substance involvement screening test (ASSIST). *Addiction*. 2008;103(6):1039-1047.
81. Stringfellow EJ, Kim TW, Gordon AJ, et al. Substance use among persons with homeless experience in primary care. *Substance abuse*. 2016;37(4):534-541.
82. Nease DE, Malouin JM. Depression screening: a practical strategy. *Journal of Family Practice*. 2003;52(2):118-126.
83. Robinson CD, Rogers CR, Okuyemi KS. Depression symptoms among homeless smokers: effect of motivational interviewing. *Substance use & misuse*. 2016;51(10):1393-1397.
84. Keogh C, O'Brien KK, Hoban A, O'Carroll A, Fahey T. Health and use of health services of people who are homeless and at risk of homelessness who receive free primary health care in Dublin. *BMC health services research*. 2015;15(1):58.
85. Bebbington P, Nayani T. The psychosis screening questionnaire. *International Journal of methods in Psychiatric research*. 1995;
86. Johns LC, Cannon M, Singleton N, et al. Prevalence and correlates of self-reported psychotic symptoms in the British population. *The British Journal of Psychiatry*. 2004;185(4):298-305.
87. Ganesh A, Campbell DJ, Hurley J, Patten S. High Positive Psychiatrie Screening Rates in an Urban Homeless Population. *The Canadian Journal of Psychiatry*. 2013;58(6):353-360.
88. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*. Sep 1991;86(9):1119-27.

89. DiClemente CC, Prochaska JO, Fairhurst SK, Velicer WF, Velasquez MM, Rossi JS. The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. *J Consult Clin Psychol*. Apr 1991;59(2):295-304.
90. Snow MG, Prochaska JO, Rossi JS. Stages of change for smoking cessation among former problem drinkers: a cross-sectional analysis. *J Subst Abuse*. 1992;4(2):107-16. doi:0899-3289(92)90011-L [pii]
91. Biener L, Abrams DB. The Contemplation Ladder: validation of a measure of readiness to consider smoking cessation. *Health Psychol*. 1991;10(5):360-5.
92. Nelson DB, Partin MR, Fu SS, Joseph AM, An LC. Why assigning ongoing tobacco use is not necessarily a conservative approach to handling missing tobacco cessation outcomes. *Nicotine Tob Res*. Jan 2009;11(1):77-83. doi:10.1093/ntr/ntn013
93. Hedeker D, Mermelstein RJ, Demirtas H. Analysis of binary outcomes with missing data: missing = smoking, last observation carried forward, and a little multiple imputation. *Addiction*. Oct 2007;102(10):1564-73. doi:10.1111/j.1360-0443.2007.01946.x
94. Glaser B, Strauss A. *The discovery of grounded theory: Strategies for qualitative research*. Aldine; 1967.
95. Elo S, Kyngas H. The qualitative content analysis process. *J Adv Nurs*. Apr 2008;62(1):107-15. doi:JAN4569 [pii]

10.1111/j.1365-2648.2007.04569.x
96. Miles MB, Huberman AM. *Qualitative data analysis: An expanded sourcebook*. 2nd ed. Sage; 1994.
97. Trochim WMK, Donnelly JP. Qualitative and Mixed Methods Analysis. *The Research Methods Knowledge Base*. 3rd ed. Thomson; 2007.
98. Creswell JW, Plano Clark VL. Chapter 7: Analyzing and interpreting data in mixed methods research. *Designing and Conducting Mixed Methods Research*. 2nd ed. Sage; 2011.
99. FDA. Laboratory analysis of varenicline products. Accessed November 11th, 2021.
100. Baggett TP, Campbell EG, Chang Y, Magid LM, Rigotti NA. Posttraumatic Stress Symptoms and Their Association With Smoking Outcome Expectancies Among Homeless Smokers in Boston. *Nicotine Tob Res*. Jun 2016;18(6):1526-32. doi:ntv238 [pii]

10.1093/ntr/ntv238
101. Center for Tobacco Treatment Research & Training, University of Massachusetts Medical School. Basic Skills for Working with Smokers - Online Course. Accessed March 28, 2017.
102. Tobacco Treatment Specialist (TTS) Core Training , University of Massachusetts Medical school. Accessed February 17, 2021.
103. World Health Organization. Taking stock: Task shifting to tackle health worker shortages. Geneva: World Health Organization; 2006.
104. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat*. 1992;9(3):199-213.
105. Zanis DA, McLellan AT, Cnaan RA, Randall M. Reliability and validity of the Addiction Severity Index with a homeless sample. *J Subst Abuse Treat*. Nov-Dec 1994;11(6):541-8.
106. Argeriou M, McCarty D, Mulvey K, Daley M. Use of the Addiction Severity Index with homeless substance abusers. *J Subst Abuse Treat*. Jul-Aug 1994;11(4):359-65.
107. Drake RE, McHugo GJ, Biesanz JC. The test-retest reliability of standardized instruments among homeless persons with substance use disorders. *J Stud Alcohol*. Mar 1995;56(2):161-7.
108. The Belmont Report: Ethical Principls and Guidelines for the Protection of Human Subjects of Research. United States, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; 1979.

109. Okuyemi KS, Goldade K, Whembolua GL, et al. Motivational interviewing to enhance nicotine patch treatment for smoking cessation among homeless smokers: a randomized controlled trial. *Addiction*. Jun 2013;108(6):1136-44. doi:10.1111/add.12140
110. U.S. Department of Health & Human Services. The Health Benefits of Smoking Cessation: a report of the Surgeon General. U.S. Department of Health & Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. DHHS Publication No. (CDC) 90-8416; 1990.
111. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. . Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
112. Siu AL, Force USPST. Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. Oct 20 2015;163(8):622-34. doi:10.7326/M15-2023
113. Jonas MA, Oates JA, Ockene JK, Hennekens CH. Statement on smoking and cardiovascular disease for health care professionals. American Heart Association. *Circulation*. Nov 1992;86(5):1664-9.
114. American Lung Association. Tobacco Cessation & Prevention. Accessed September 22, 2016.
115. American Cancer Society. Stay Away from Tobacco. Accessed September 22, 2016.
116. Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM, Reid N. Effects of contingency management and bupropion on cigarette smoking in smokers with schizophrenia. *Psychopharmacology (Berl)*. Apr 8 2011;doi:10.1007/s00213-011-2282-8
117. Etter JF, Schmid F. Effects of Large Financial Incentives for Long-Term Smoking Cessation: A Randomized Trial. *J Am Coll Cardiol*. Aug 23 2016;68(8):777-85. doi:10.1016/j.jacc.2016.04.066
118. Etter JF. Financial incentives for smoking cessation in low-income smokers: study protocol for a randomized controlled trial. *Trials*. 2012;13:88. doi:10.1186/1745-6215-13-88