Metabolism Informed Smoking Treatment in Medicaid and Medicare Patients: The MIST RCT

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1.0 Background

Every year smoking kills almost 500,000 Americans and costs the nation 1.6% of the gross domestic product. [1] Over 20 million U.S. smokers attempt to quit smoking annually, yet two-thirds or more are not treated with proven cessation medications. [2, 3] When medication is provided, it is not biologically tailored. Metabolism Informed Smoking Treatment (MIST) increases precision of smoking treatment by leveraging speed of nicotine metabolism to optimize pharmacotherapy.

MIST matches the right patient to the right drug. MIST seeks to overcome one of the most serious limitations of the current standard of care for smoking treatment, which is the generic (i.e., non-biologically tailored) nature of medication selection. [4] About 60% of smokers are "normal" (i.e., faster) metabolizers of nicotine for whom nicotine replacement therapy (NRT) produces sub-optimal results. [5] Yet about 90% of all smokers who use cessation medication use nicotine replacement, resulting in widespread therapeutic mismatch. [2] For these "normal" metabolizers, Varenicline shows evidence of improved quit rates over NRT among normal, but not slow, metabolizers. [5]

The nicotine metabolite ratio -- NMR --is a validated, reproducible biomarker for nicotine metabolism. A large body of research has established the nicotine metabolite ratio (NMR) as a validated biomarker of nicotine metabolism that predicts smoking behavior and therapeutic response to cessation pharmacotherapy. Measurements of plasma NMR are reliable across analytical methods and laboratory sites, unaffected by sampling time or storage temperature, and for regular daily smokers, are consistent despite variation in smoking. [6-8] Finally, NMR reflects both genetic and environmental influences on nicotine metabolism, and therefore may have even greater predictive power than genetic markers. [9]

NMR is associated with smoking-related traits and overall treatment response. Fast/normal (i.e., higher NMR) vs. slower metabolizers smoke more cigarettes per day, [10-12] smoke more intensely, [13] exhibit enhanced abstinence-induced neural responses to smoking cues in craving-specific brain regions,[14] and have greater thalamic nicotinic receptor availability in early abstinence. [15] Collectively, these metabolism-associated physiologic differences explain in part why fast/normal metabolizers have greater difficulty in quitting and consistently have the lower quit rates at end-of-treatment. [16-18]

Centers for Medicare and Medicaid (CMS) -enrolled smokers bear a disproportionate burden of smoking related illness and many want to quit smoking yet are undertreated.
Medicaid. At 37%, the national smoking prevalence among Medicaid enrollees far exceeds the national average in the general population. [19] In Tennessee, smoking prevalence among Medicaid (TennCare) adults is higher than among privately-insured low-income TN residents and higher than the 22.1% average statewide. [19]

As many as half of Medicaid-insured smokers make a quit attempt each year, but, on average, only about 6.5% are successful, [20] due in part to the low rates of use of covered smoking cessation pharmacotherapy (< 10%). [19] This low rate of medication use reflects low knowledge among patients (36%) and providers (60%) about smoking cessation treatment benefits. [21] Expansion of medication coverage increases the likelihood that enrollees will attempt to quit (from 10.2% to 20.3%), utilize the medication benefit, and quit successfully (from 3.8% to 9.1%). [20, 22] Concomitant with this reduction was a statewide decrease in the hospitalization rate of Medicaid covered patients. [23]

Medicare. Medicare smokers are generally older and as expected, smoke at rates that tend to be lower than the national average (10.2%-12.5%), [24, 25] yet they are heavily burdened by smoking-related disease and report significantly lower physical and mental health related quality of life relative to non-smokers of similar age. [26] Over four of every ten Medicare smokers attempt to quit each year, yet quit rates have remained stagnant in recent years, due in part to low rates of use of pharmacotherapy among smokers with pharmacy benefits (16% overall: 9% varenicline, 4% bupropion, 1% NRT alone, 2% some combination). [27, 28] Similarly, Medicare enrollees quit smoking twice as often when they receive quitline counseling and pharmacotherapy, compared to Usual Care consisting of self-help materials (19.3% vs. 10.2%). [29] In a population of smokers hospitalized and counseled by the tobacco treatment service, Medicare enrollees exhibited higher willingness than commercially-insured patients to accept smoking treatment.[30] Finally, CMS has the infrastructure for the widespread implementation of MIST nationwide to help millions of those who have prescription medication benefits and who could be seamlessly offered this precision approach by their health care provider.

2.0 Rationale and Specific Aims

2.1 Rationale

Smoking is the leading preventable cause of disease and death in the world and the US. [31] Smokers who receive insurance coverage through the Centers for Medicare and Medicaid (CMS) are at high risk of smoking-related disease yet are profoundly undertreated despite having pharmacy benefits for FDA-approved smoking cessation medications. [20, 24] We propose Metabolism-Informed Smoking Treatment (MIST), a precision approach that biologically tailors medication to nicotine metabolism, in hospitalized smokers enrolled in CMS. Nicotine metabolism predicts nicotine dependence, cessation success, and outcomes with pharmacotherapy. [5, 10-13, 16-18]

Nicotine is rapidly metabolized in the liver primarily by the cytochrome P450 enzyme CYP2A6 to cotinine, which is further metabolized to 3-hydroxycotinine (3-HC) by CYP2A6. [32, 33] The NMR (ratio of 3-HC to cotinine) reflects CYP2A6 activity and the rate of nicotine metabolism, and to date is the only biomarker to

predict a therapeutic response in a smoking cessation RCT. [5, 10] Overall, about 2/3rd of smokers are "normal" metabolizers, while ~1/3 are "slow" metabolizers. [5] In a landmark RCT, among normal metabolizers, varenicline doubled cessation rates over NRT (patch) at end of therapy (39% vs. 23%) and 6 months (23% vs. 13%). [32, 34] Slow metabolizers had more side effects but no cessation benefit from varenicline. The number needed to treat (NNT) for one normal metabolizer to quit was 4.9 for varenicline vs. 26 for NRT patch, establishing a strong scientific premise to pair normal metabolizers with varenicline and slow metabolizers with NRT. [5]

Informed by our preliminary data, we propose a scientifically rigorous RCT design of approximately 1,000 adult CMS beneficiaries or those with prescription coverage, who are daily smokers hospitalized at Vanderbilt University Medical Center (VUMC) to compare effects of MIST vs. UC on: abstinence (1° aim), implementation in clinical practice (2° aim), and health care utilization and mortality (exploratory). All participants will receive UC for tobacco treatment, including: (1) bedside tobacco consult; (2) a prescription for varenicline or NRT; and (3) automated phone calls via TelASK to promote engagement after study enrollment. Medication prescriptions will be NMR-guided for MIST participants and patient-provider selected for UC participants. Type of NRT (e.g., inhaler, gum, patch, etc.) will be informed by insurance type. For example, some plans in Medicare Part D cover only prescription NRT (inhaler, nasal spray) while most state Medicaid programs only cover over-the-counter (OTC) meds (e.g., patch, gum, lozenge). The research team will work with PCPs and their staff to facilitate smoking treatment after study enrollment and will track pharmacy records for PCP-generated prescriptions for patients who continue smoking. PCPs of patients in MIST will be given the NMR results, while PCPs of UC participants will not. Phone surveys will be conducted at approximately 1, 3, 6, and 12 months to assess medication adherence and smoking status, with biochemical validation of abstinence at 6 and 12 months via salivary cotinine for those not using nicotine-containing products at the time of testing. For those using nicotine-containing products at the time of testing, carbon monoxide or anabasine (if available) will be used. See Table 2 for cut-off values. If feasible within the study timeline and staffing, health care utilization and mortality will be tracked passively over 12 months via existing databases (e.g., Tennessee Hospital Discharge Data System, TN HDDS) via exploratory Aim 3. Investigators have complementary and broad expertise to conduct MIST, the first large RCT to incorporate NMR results into clinical treatment of smoking.

2.2 Specific Aims

The specific aims of the study will compare the effects of MIST vs. UC on:

- AIM 1: Abstinence as defined by biochemically-verified self-reported 7-day point prevalence abstinence at 6 m (1° study outcome) and 12 m (2° outcome).

- H1: MIST will produce higher abstinence rates.

- AIM 2: Implementation in clinical practice as reflected by: (2a) Patient's self-reported medication adherence at 1, 3 m; (2b) PCP prescription for smoking cessation medication any time after study enrollment, controlling for participant's abstinence; and (2c) whether the prescription is matched to NMR.
    - H2: MIST will produce higher rates of adherence, PCP medication prescription after study enrollment, and NMR-matching of prescriptions.

- AIM 3: A healthcare composite outcome (exploratory) comprised of healthcare utilization visits (ER & hospitalizations) and mortality (all-cause & cause-specific) ascertained via the VUMC EHR, CMS databases, state vital records, and TN HDDS.
    - H3: MIST will reduce health care utilization and death compared to UC.

2.3 Significance – Projected Impact of Completed Aims

Results could establish MIST as a fundamentally new framework for treatment of smoking, with significant scientific and clinical implications. Given that varenicline and nicotine replacement differ profoundly in cost and side-effect profiles, MIST has the potential to optimize overall population outcomes including cost-effectiveness, which is an important future direction for this research. Results could elucidate and reduce disparities in cessation and smoking-related illness. [35] From a population health perspective, MIST implementation in CMS could positively impact about 20 million smokers.

MIST is the first full scale RCT to test the impact of a metabolism informed approach to smoking treatment in clinical practice. This project will enroll smokers from VUMC, a Learning Healthcare System and national leader in precision medicine with the infrastructure to implement the MIST intervention. While precision medicine has become a popular scientific trend, this team recognizes the need to rigorously test interventions such as MIST to accurately and responsibly determine their utility for clinical care. If implemented broadly, Metabolism Informed Smoking Treatment (MIST) could double abstinence for 6 of every 10 smokers, yet its efficacy has not been tested in clinical practice. MIST may especially help populations who bear a disproportionate burden of smoking-related illness and are undertreated despite having full coverage of smoking cessation pharmacotherapy, such as CMS beneficiaries who smoke.

3.0 Previous Human Studies

Data establishing the scientific premise of the current proposal come from a large (N = 1,246) prospective placebo-controlled RCT, led by our team member Dr. Tyndale, that randomized subjects by nicotine metabolite ratio (NMR) group (i.e., "normal" vs "slow," using a threshold of 0.31) to placebo, nicotine patch, or varenicline. [5] Varenicline improved quit rates over NRT at end of therapy (OR 1.89, 95% CI 1.02–3.45) and 6 months (OR 2.17, 95% CI 1.38–3.42) (all p=0.001) among normal, but not slow, metabolizers. In contrast to the current proposal, the prior study treated NMR as an explanatory variable and did not incorporate knowledge of nicotine metabolism into selection of smoking cessation medication or any part of clinical treatment.

To demonstrate feasibility of this proposal, we conducted and published a pilot RCT of 81 adult daily smokers with medical comorbidity to a metabolism-informed intervention vs. a robust control, established infrastructure to track participants, and collected outcome data. [36] Participants reported perceptions of the metabolism-informed intervention, underwent blood draw for NMR, and received expert cessation counseling. For intervention participants, medication selection was informed by NMR result (normal (≥0.31) vs. slow (< 0.31)) using the threshold by Tyndale and colleagues. [5] The primary outcome was feasibility of offering NMR in a clinical population, reflected by attitudes toward the precision intervention and by match rates between NMR and medication. Secondary endpoints (cessation, confidence, medication use, smoking status) were assessed over 6 months for feasibility. The median NMR for slow metabolizers was 0.22 [0.18–0.27] and for normal metabolizers was 0.54 [0.38– 0.82], similar to the distribution observed in the literature.[5] Over 90% of participants endorsed the idea of metabolism informed care and all but two were prescribed medication. Despite very high varenicline prescription rates of ~60% in both treatment arms, NMR-medication matching was markedly higher among intervention (36/43; 84%) versus control (21/36; 58%) participants. Put another way, 42% of control participants were "mismatched," as compared to only 16% in intervention (p = 0.02). At the 6 month follow up time point, 80% of participants were reached. While this pilot RCT was not powered for abstinence, medication adherence, or other cessation-related outcomes, these were assessed as part of the feasibility of outcome data collection. Self-reported rates of medication use and side effects at 3 months, and 7-day point prevalence abstinence at 6 months, did not differ statistically between treatment arms. From this pilot study we concluded that: (1) Smokers viewed the metabolism informed treatment favorably and were willing to use medication based on NMR test results, with 3-fold increased concordance (matching) between nicotine metabolism status and medication in the intervention arm; at the same time, (2) Nearly 1/2 of patients in UC received medications that were not matched with their NMR, underscoring the generic nature of UC despite high prescription rates of varenicline in both treatment arms of the study.

4.0 Detailed Study Overview

Eligible participants are consented and enrolled into the study during their inpatient hospital stay, participants may also be enrolled in the ER and observation unit. Potential participants may also be recruited from procedural or other same day settings, such as same day surgeries, pre-op or admission planning visits, or health screenings involving imaging or procedures, such as lung cancer screening. This process includes: (1) Screening, enrollment, randomization; (2) Post-enrollment treatment support; (3) Outcome ascertainment via survey, biochemical samples, and passive follow up using health system databases.

1. Screening, enrollment, randomization

- Screening & enrollment
    - Initial Certified Tobacco Treatment Specialist (CTTS) (tobacco counselor) assessment and tobacco cessation counseling (with initial screening consent for NMR).
    - Confirmation of eligibility and assessment of inclusion and exclusion criteria by study RA, including NMR result and verification by pharmacy personnel through procedures such as insurance test claims.
    - The screening consent for the NMR test will occur before the main consent for study enrollment. To accommodate patients who are eligible for the study but who request more time to consider enrollment, study staff may obtain screening consent and then complete remaining enrollment steps such as blood draw at a later time (e.g., after study enrollment/clinic visit).
    - Patients will be randomized after study staff ensures they have met all criteria, including a valid NMR result. Blood for NMR testing may be collected via a fresh blood draw or using stored clinical samples. The NMR results will be analyzed after study staff completes the screening consent process with the patient. Study enrollment forms may be completed remotely, as needed, due to the time constraints of meeting participants in-person.
    - Study staff verifies patient contact information as part of the enrollment process. Due to time constraints, verification of contact information will be prioritized immediately after the screening consent process.
    - If the main consent process takes place remotely, the consenting structure will remain the same (i.e. screening consent will be completed prior to the main consent). In this case, study staff will electronically provide a copy of all applicable study documents to the patient prior to verbally reviewing all elements of the consent. If no electronic delivery of the main consent is possible, a paper copy of the main consent will be provided in-person or mailed to the patient before verbal review over the phone.
    - Baseline survey may be completed remotely, as needed, due to the time constraints of meeting participants in-person.
    - Participants will be compensated with $10 for the screening blood draw and $40 for completion of the baseline survey.

- Randomization
    - Randomization will take place after a valid NMR has resulted. As noted above, in the case that a participant meets all other criteria, but NMR is not resulted, a patient may be consented but will not be randomized until after the NMR is resulted.
    - In the rare event that an NMR sample results as invalid (nicotine unable to be detected in sample) after the participant has been enrolled, the study team will obtain a backup sample within approximately a week of study enrollment. This sample will either be a stored clinical sample or the study team will coordinate a new blood draw. As needed, a courier service will be used to retrieve and deliver this sample.
    - Study medication will be provided by a VUMC or outside pharmacy after study enrollment either in-person or mailed to the participant's home. Participants who are unable to pay for their insurance co-pays for smoking cessation medication may be referred to existing programs at Vanderbilt University Medical Center to facilitate obtaining medication. In the infrequent instance where charges related to the study are mistakenly billed to the participant, the study team will reimburse the participant via a gift card.
    - Participant will be provided with study information including a copy of the consent document and, for those randomized to the MIST arm, information on the NMR test.

2. Post-enrollment treatment support

Beginning at approximately 3 days and weeks 2, 4, 6, 8, 10, and 12 post-enrollment the participant will receive automated Interactive Voice Response **(IVR) support calls from TelASK** to assess smoking status and medication receipt/adherence. Participants may also opt to speak with a **study Tobacco Treatment Specialist** if needed. At 6 months, all participants (regardless of smoking status) will be offered a second cycle of IVR calls. To maintain the study timeline, participants recruited in the final year of the study will not be offered the second cycle of IVR calls.

3. Outcome ascertainment

At approximately 1-, 3-, 6-, and 12-months participants will complete **follow up surveys** via:

- Text message or email, based on the participant's preference, containing a link to the REDCap follow up survey. If the participant prefers phone contact, a study team member will call. Compensation is $20 per completed survey. If participants fail to respond to 6, 12 month surveys, they may be contacted by phone call or mailed survey.
- If the participant cannot remotely complete items related to follow up. including surveys, we will make all efforts to coordinate with the patient during any pending appointments at VUMC so they can complete their

survey on a day when they are already scheduled to be at VUMC (e.g. study RA will travel to the One Hundred Oaks clinic of other VUMC clinics to meet participant).

When study staff is unable to reach participants for follow up surveys after several attempts, the next step will be to reach out to alternative contacts provided by the participant at enrollment. An alternative contact that is a reliable close relative (i.e., spouse, significant other, or caregiver) can opt to complete a survey on the participant's behalf as a proxy. This survey will be considered complete "by-proxy" in the study database.

Biochemical Validation of self-reported tobacco abstinence at 6 and 12 months.

- Participants are asked to complete a carbon monoxide (CO) test or salivary cotinine test to confirm quit smoking status if they indicate on the survey that they have quit smoking. $100 will be offered for completion of biochemical validation at each of the 6 and 12 month timepoints. $50 will be offered for travel reimbursement at each of the 6 and 12 month timepoints if patients complete biochemical validation in person.

Compensation. Total compensation for full study participation is $430.00.

5.0 Study Procedures

5.1 Tobacco Treatment Service Consult

The VUMC inpatient Tobacco Treatment Service (TTS) will typically be the first point of contact for recruitment. ViTAL (the Vanderbilt Center for Tobacco, Addiction and Lifestyle) Center research staff may also visit smokers directly to initiate the NMR blood draw, followed by the tobacco clinician (CTTS) consult. The TTS program is an evidence-based clinical service for Vanderbilt University Hospital (VUH) hospitalized patients who smoke. [37] Patients admitted to VUH reach the TTS as follows: (1) Routine smoking status documentation in the EHR at admission by a nurse produces a daily list of smokers which the CTTS accesses in Epic; (2) Following an "opt out" design, a CTTS visits smokers to offer brief bedside counseling and medication support. Patients may opt to decline the consult. For each consult, the CTTS reviews the medical chart and at the bedside, assesses tobacco use patterns, offers counseling, and recommends FDA-approved smoking cessation pharmacotherapy to manage nicotine withdrawal and promote cessation. A typical bedside or phone discussion lasts 15-20 minutes.

5.2 Screening and Recruitment

Screening will take place by phone or in-person. During the course of a tobacco treatment consult, the CTTS will screen each smoker for preliminary study eligibility using the Counselor Screening Form (CSF), including consent to speak with study

staff. The CTTS will also inform the patient that there is a mandatory blood test required to participate in the study. The CTTS or study staff (research assistant (RA)) will obtain consent on the Screening Consent Form to perform the NMR blood test. The CTTS and/or RA will check for an existing and valid NMR result in the patient's EHR. If no previous NMR results are available, the study team may order an NMR test to be performed on a blood sample that has already been obtained and is available for testing. The study team may also order a new blood draw for the NMR.

The RA will visit or call those patients who are preliminarily eligible based on the CSF to verify eligibility, explain the study in detail using a written handout, and obtain informed consent. Screening for eligibility will include reviewing the patient's chart in the EHR (e.g., review of CTTS progress note, admission notes, and other medical records as needed) and completion of the RA Screening Form (RASF). As needed, the RA will also query the care team to determine exclusion criteria. If the patient wishes to have more time to consider study participation, he or she will be given the name of the RA and study phone number. Because hospital lengths of stay tend to be short (3-5 days), it is possible that the patient will be discharged before being able to fully enroll in the study.

5.3 Inclusion Criteria

Inclusion Criteria

- 18 years old or older
- be enrolled in or pending approval for an insurance plan that supports prescription coverage for smoking cessation medication (including Medicare part D, Medicaid, private insurance, Federal or other governmental, or other insurance) or willing and able to purchase smoking cessation medication and pay for healthcare out of pocket to facilitate delivery of medications
- have a regular provider/PCP or have access to a free or low cost clinic for regular clinical care that can prescribe smoking cessation medication; if patient does not have a PCP, the study team may collaborate with the patient to establish a primary care provider
- agree to quit or try to quit smoking upon study enrollment
- be a daily smoker when smoking normally during the month prior to entering the study
- be medically eligible to use varenicline*
- be medically eligible to use nicotine replacement therapy **
- have received medication recommendations from a tobacco counselor
- agree to take smoking cessation medication (i.e., varenicline OR nicotine replacement therapy) home and consider using it
- have a cell phone or landline that can be reached directly (i.e., without transfer)
- have a permanent address where they live and can receive mail
- estimated life expectancy of at least one year or greater

*Medical eligibility to take varenicline is defined by absence of the following:

- Serious brain condition that impairs cognition (including but not limited to dementia, delirium, brain tumors/metastases, uncontrolled seizures (i.e., seizures within the past 3 mo.))
- pregnancy/planning to become pregnant/breastfeeding in the next year
- history of allergic reaction to varenicline
- unstable/uncontrolled mental health condition:
    a. altered mental status (e.g., delirium, hallucinations) ***OR***
    b. serious psychiatric symptoms in the past 6 months as defined by suicidal ideation or attempt, hospitalization or ED visit involving a psychiatric condition (e.g., depression, anxiety, bipolar, schizophrenia, schizoaffective disorder, PTSD, substance use (e.g., overdose, other related) ***OR***
    c. changes in psychiatric medication within the past 3 months
- if alcohol use; history of blackouts or seizures with drinking

** Medical eligibility to use nicotine replacement therapy is defined by absence of the following:

- unstable from cardiovascular perspective
- current or history of Buerger's disease (also called thromboangiitis obliterans)
- pregnant/planning to become pregnant/breastfeeding in the next year

5.4 Exclusion Criteria

Exclusion Criteria

- insufficient time to perform and complete the enrollment process
- barrier to effective communication (including low English proficiency)
- not cognitively able to participate in the study
- too ill, on hospice, or physically unable to participate in the follow-up process
- previously completed the MIST study or is currently enrolled in a quit smoking study that involves a medication-based treatment
- estimated life expectancy of less than one year

5.5 Informed Consent

Informed consent for NMR Screening: Potentially eligible smokers who are counseled in the hospital or by phone by a CTTS will be told briefly about the study and, if interested, the CTTS will obtain a signed screening consent from the patient for NMR sample. An RA may also obtain screening consent for NMR.

Informed consent for full study enrollment: Study staff will perform informed consent. Potential participants will be told that their participation is completely voluntary, and that they can opt out at any time or refuse to participate in any portion of the study. During the consent process, potential participants will be informed of all study procedures, including possible side effects of medications used. The informed consent document will state that the study is being done as a collaboration between VUMC and TelASK. Potential participants will be informed that in order to make the phone calls, TelASK will be given information such as their name, study ID, phone number, sex, preference for time of call, and the date that they are discharged from the hospital or enrolled in the study. There is a small but potential risk of data breach with this transfer of information. However, TelASK-generated IVR calls are becoming an integral part of the clinical care of smoking in multiple healthcare systems across North America. The consent will indicate that participants may be invited to participate in future studies.

Whenever possible, the consent process will be conducted electronically using REDCap, a secure, web-based, HIPAA-compliant, data collection platform. REDCap has a user management system that allows project owners to grant and control varying levels of access to other users (e.g., viewing of data collection instruments and data may be specified as read only). Patient signatures can be obtained as typed or written signature via stylus/cursor. After consenting, patients will be provided with a printed or e-mailed pdf copy of the consent document or a web link to the consent. The web link provides access to a ROCKET site containing their signed consent form. Signed consent documents will NOT be housed electronically on ROCKET.

5.6 Baseline Survey and EHR Data (see Table 1, baseline column)

Baseline data are collected from the medical chart, Counselor Screening Form, RA Screening Form, as well as the Baseline Survey. Data collection will include items such as: Sociodemographic factors (age, sex, education, race/ethnicity, employment, living situation, health insurance type), admitting diagnosis category (cardiac/non-cardiac), tobacco use history (years of smoking; use of other tobacco products; Heaviness of Smoking Index, [38] measures of nicotine dependence (cigarettes smoked/day in month before admission and time to first morning cigarette)), rules for smoking in home, [39]alcohol use (AUDIT-C a 3-item survey assessing frequency and quantity of alcohol consumption that predicts problem drinking), [40] depressed mood and anxiety (PHQ-4, a validated screening test for depression and anxiety),[41] intention to remain abstinent from tobacco after study enrollment, pre-existing medical conditions, past use of FDA-approved smoking cessation medications, confidence to quit [42, 43], social support for quitting, perceived health risks of smoking and benefits of quitting,[44] optimism/pessimism as captured by the Life Orientation Test,[45] delay discounting Task (5 Trial Delay Discounting,

Tangney et al. Brief Self-Control Scale), [46-48] and detailed contact information for the patient and an alternative contact.

Some of these data are routinely collected by the CTTS and entered into the EHR and/or TTS electronic database; other data are collected by the study RA using a password protected iPad or computer connected to the hospital's secure wireless connection. Study RAs will administer the baseline questionnaire via REDCap[49] (or paper, if needed). All baseline data are entered securely into REDCap. If needed during a power loss, paper forms will be used during enrollment and stored securely in a locked cabinet that only study staff will have the ability to access.

5.7 Baseline blood sample collection

During screening/enrollment, we will attempt to collect a blood sample of approximately 15 ml (3 teaspoons) at the bedside or at an outpatient lab such as VUMC OHO or Cool Springs by clinical phlebotomy/study staff. Blood samples will be used for determination of nicotine and metabolites (for NMR) and future analysis of genetics and other potentially relevant biological markers. Participants will be asked to consent for these data to be collected for the proposed research project and for potential future research. Participants will be advised that blood may be discarded under certain circumstances (e.g., if they elect to not enroll in the study or are deemed ineligible after the NMR blood draw).

Blood sample for NMR test: Often temporarily stored blood is available through the Clinical Pathology Laboratory that can be used for NMR testing. When no stored blood is available, or if time constraints preclude locating and pulling stored blood, a fresh blood sample will be collected for NMR testing. Stored blood may be used when a patient's health precludes a fresh blood draw, not limited to anemia (where hemoglobin lab results are less than 8), hemophilia, and other appropriate disorders or states.

Blood sample for future potential genetic and other analyses:
The NIH's precision medicine initiative, All of Us, aims to understand how genetics, in conjunction with a person's environment and lifestyle, can optimize prevention and treatment of illness. The GSCAN results recently published in Nature Genetics [50] identified hundreds of new genetic variants related to smoking initiation, rate, maintenance, cessation, and substance use. New information continues to become available regarding the role of genetic variation in smoking cessation and response to pharmacotherapy and substance use more broadly. In instances where stored blood is used and supply is limited, NMR test will be prioritized. If a sufficient blood sample cannot be obtained for future genetics research, study staff will collect saliva instead.

5.8 Randomization

Patients can be randomized into the study once the NMR test has resulted. Randomization will be stratified on three factors: (1) primary admitting diagnosis (cardiac vs. other); (2) cigarettes/day (≥10, <10); (3) primary insurance (Medicaid, Medicare with Part D, Private Insurance, Federal/Other Governmental/Other Insurance); and (4) NMR status ("normal"/"slow") to ensure that the treatment groups are balanced. After the patient enrolls, the RA will be directed to the electronic randomization screen in REDCap, which, once submitted, automatically assigns the participant to a randomization group.

Blinding: The nature of the study precludes blinding of patients or research staff to the study condition.

Participants will receive a handout describing their assigned treatment. For those randomized to the MIST (precision) arm, the handout will include information on the NMR result and recommended medication. In the event that a participant is enrolled before a valid NMR result is received, study staff may contact the participant via phone/text/email (per participant preference) to notify of randomization status and initiate post-randomization procedures including facilitation of smoking cessation medication. Those randomized to the Usual Care arm will receive their NMR result at study completion, 12 months post-study enrollment; participants in the Usual Care arm who withdraw from the study will not be provided precision care information.

5.9 Outcome Assessments – Surveys (Table 1) and Biochemical Samples (Table 2)

Follow up surveys: (**Table 1)** See Page 32 for full table. A brief follow up survey will be sent to participants through a REDCap-enabled Twilio survey link via email/text message based upon participants preference as stated at enrollment. The surveys will be sent to participants at approximately 1, 3, 6, and 12 months after study enrollment. For completeness, smoking status and medication usage outcomes will be assessed at all follow-up time points. Participants who do not respond to survey invites sent through email or text will be contacted by phone and mail. If the participant cannot complete the follow up survey remotely, we will make all efforts to coordinate with the patient during any pending appointments at VUMC so they can complete their survey on a day when they are already scheduled to be at VUMC (e.g. study RA will travel to the One Hundred Oaks clinic of other VUMC clinics to meet participant) If these modes are insufficient to complete surveys, alternative contacts (participant's proxy) will be contacted. When needed, , study staff call participants to administer the survey, making approximately 24 attempts over 4 to 8 weeks. If unsuccessful, participants may be mailed an abbreviated survey containing only the primary and secondary outcome measures. We have successfully administered similar questionnaires for prior studies of hospitalized smokers and low-income smokers residing in the Mid-South, Mid-Atlantic, and New

England regions. Study staff also offer to meet participants at their clinic visits for convenience. Study staff may also extract information from the EHR fields such as smoking status and cigarettes per day, use of other tobacco products, and smoking cessation medication use.

Biochemical Samples

Aim 1: Biochemical Verification of Self-Reported Abstinence (Table 2, Row 1)

For participants who self-report abstinence at the 6 month and/or 12 month follow up surveys, study staff will attempt to biochemically-verify the self-report. Based on prior experience with challenges in obtaining biochemical verification, there will be several options including: (1) saliva cotinine (in- person or mailed); (2) end-expired carbon monoxide (in-person or remote) if participants are unwilling or unable to verify with cotinine (e.g., actively using NRT). Standard saliva cotinine kits will be analyzed by Salimetrics Laboratory or other comparable lab. Smoking abstinence can also be confirmed through in-person or remote carbon monoxide (CO) testing (if a participant is on NRT). If a participant is unable to complete an in-person CO, then a personal CO device (such as a CoVita iCO Smokerlyzer) may be mailed to the participant to complete the CO reading remotely. We have successfully used this protocol for mailed cotinine samples and CO testing in the past. Smoking abstinence will be defined conservatively according to recommended standards.

The following cessation milestones will be assessed in addition to point prevalence abstinence (PPA):

i. *Initial abstinence* is defined as the first instance in which the participant refrains from smoking for at least 24 hours; duration of initial abstinence will also be assessed.
ii. *Initial lapse,* defined as the first episode of ANY smoking, even a puff, after achieving initial abstinence, will also be assessed.
iii. *Continuous abstinence* is defined as no smoking, even a puff, since study enrollment (i.e., achieved PPA at 1, 3, 6, and 12 mo +no smoking in between surveys + biochemical validation of self-reported (SR) PPA at 6, 12 mo). Participants who are unable to biochemically verify abstinence will be assumed to be smoking, by convention, but sensitivity analyses will consider a range of possible odds ratios (1, 2, and 5) linking loss to follow-up and smoking. [51]

Table 2: Main Outcome Measures by Study Aim			
Outcome	**Measure**	**Data sources**	
		Survey	**Other source**
AIM 1: Abstinence	SR at 1, 3, 6, 12 m **Biochem. validation at 6 m (primary study outcome) and** 12 m*	X	Biochemical validation at 6, 12 m* via saliva cotinine <10 ng/ml or expired CO <10ppm
AIM 2: Medication adherence	SR at 1, 3, 6, 12 m	X	CMS pharmacy records
AIM 2: PCP engagement	PCP prescription for smoking cessation medication any time after study enrollment	X	EHR, CMS pharmacy records
AIM 3: Healthcare composite	Hospitalization, ED visits, deaths	---	EHR, TN state vital records, TN HDDS, CMS database

AIM 2 - Clinical Implementation as assessed by Medication use and PCP Engagement (Table 2, Rows 2, 3). These outcomes probe the extent to which MIST vs UC are taken up and implemented by patients and providers. Patient engagement is assessed by medication use and adherence. Provider engagement is assessed by writing a prescription for FDA approved medication any time after study enrollment.

a. Self-reported medication adherence over the past 7 days will be assessed via survey. Participants are asked if they have taken study medication each day and for skipped or missed doses, reasons are elicited (e.g., forgot to take it/ felt I didn't need it/experienced side effects/ felt the medication wasn't working/other, etc.). Participants are also asked about OTC and non-study medication use. Using our pilot protocol, participants are considered adherent at each survey if they report taking their medication for at least 5 of the past 7 days.

b. PCP-generated prescriptions for smoking cessation medication will be assessed by patient self-report and where possible, verified by sources such as VUMC EHR, TennCare and Medicare pharmacy data. The outcome will also be assessed in the subset of participants who self-report smoking on study surveys. Type of medication prescribed will also be tracked to calculate % concordance between NMR result and medication (i.e., % of fast metabolizers prescribed varenicline, % slow metabolizers prescribed NRT).

Health care utilization and mortality composite (Table 2, Row 4):

a. This composite clinical outcome will be assessed by passive query of the VUMC EHR, the Tennessee Medicaid (TennCare) database, and the Department of Health Hospital Discharge Data System. The composite variable includes any evidence of a documented incident inpatient hospitalization, ER visit, or death during the follow up period. Death will be defined as death due to any cause as determined by National Death Index or death certificate data from Tennessee State Vital Record Files. Cause-specific mortality will be determined via death certificates obtained from the Tennessee State Vital Records, which has death certificates for all deaths in Tennessee and for Tennessee residents who die in adjoining states. Passive surveillance of 12-month clinical composite outcomes takes place at VUMC and non-VUMC facilities, as described further below.
    i. At VUMC facilities. Hospitalization and ER visits at VUMC are tracked by Drs. Freiberg and Wells, leveraging VCREATE and V-SERCH Center resources including validated EHR algorithms to extract clinical outcomes including ER visits, hospitalizations and mortality.
    ii. At non-VUMC facilities. We have established links between VUMC EHR data and external databases including Tennessee Medicaid and the Hospital Discharge Data System (TN-HDDS). The TN-HDDS collects patient-level discharge information in visits from all hospitals licensed by the Tennessee Department of Health (TN DOH), including rehabilitation hospitals, psychiatric units within acute care hospitals, and free-standing ambulatory surgical treatment centers. Tennessee Medicaid (TennCare) maintains an extensive electronic data system and records of all their healthcare encounters, including pharmacy prescriptions filled.

b. Vital status may be ascertained by study staff reviewing VUMC medical records, utilizing automated electronic health record (EHR) deceased notifications, conducting obituary searches, participant proxy contacts, and PCP/provider offices. Death certificate data from the Tennessee Office of Vital Records may also be used to identify all deaths occurring within Tennessee, and deaths of Tennessee residents that occur in surrounding states. Vanderbilt's Health Policy Department processes these data for research and public health surveillance activities via data use agreements with the TN DOH. Finally, data from the National Death Index or related databases that include information on mortality may be queried.

MIST Ancillary study - Validation of EHR-derived smoking status with survey and biochemically-validated smoking abstinence in the MIST RCT: If EHR-derived self-reported outcomes were valid, then large health care systems and their

EHRs could become a new frontier for tobacco control including large observational studies and multisite pragmatic clinical trials. Smoking cessation RCTs conducted within a health system thus offer a unique opportunity to determine the accuracy of smoking status as captured in the EHR.

a. **AIM 1**: Using biochemical validation as the reference for abstinence at 6 months, determine the reliability of EHR-based and survey sources of smoking status among MIST trial participants. Hypothesis: EHR based smoking status and research survey smoking status will have a high sensitivity, specificity, positive predictive value and negative predictive value as compared to biochemical validation among participants in the MIST study.
b. **AIM 2**: Demonstrate the application of EHR-based smoking status in analyses of the impact of NMR-guided prescribing practice on smoking cessation in the MIST trial. **Hypothesis**: EHR-based smoking status may be incorporated into analyses that use smoking abstinence as an outcome (e.g., 7-day point prevalence abstinence (PPA) at 6 months, the primary outcome of the MIST parent trial) through either an extension of existing multiple imputation methods or through direct use of EHR-based smoking status as an outcome.

The ability to leverage electronic health records for tobacco and cancer related research would allow investigators to efficiently and powerfully examine the role of smoking, smoking cessation and cancer among diverse populations, including people actively attempting to change their smoking behavior.

5.10 Compensation

Participants can be compensated up to a total of $430 for full participation in this research study. Participants will receive $10 for the screening blood draw and $40 for completion of the baseline survey. For completion of the follow up surveys at 1, 3, 6, and 12 month study timepoints participants will receive $20 per survey. In addition to survey completion, participants who report quitting smoking on the 6 and 12 month surveys will be asked to provide either a saliva sample or complete a CO test, used for biochemical validation of self-reported abstinence. For completion of biochemical validation at the 6 and 12 month timepoints, participants will receive $100 per timepoint. $50 will be offered for travel reimbursement at each of the 6 and 12 month timepoints. Similar compensation has been used in a previous research studies and was deemed by the VUMC Institutional Review Board (IRB) to be an appropriate, non-coercive, amount of funds for involvement in a clinical research project.

5.11 Retention

Baseline visit: Retention efforts begin at baseline by ensuring that everything possible is done to maximize the likelihood of the participant enjoying the experience of participating in the study. Retention is supported by explaining the informed consent and what may happen in the study, and by collecting complete contact information, including both the address where the participant currently resides as well as multiple contact numbers if available. Participants will be asked to provide contact information for at least one alternative contact who may know their whereabouts if we are ever unable to get in touch with the participant. Alternative contacts can include friends or family members; an alternative contact who is a close relative (ie. spouse, significant other, or caregiver) can opt to be the participant's proxy. Participants will also be asked to provide an email address. The Interactive Voice Response (IVR) that all participants receive beginning 3 days after study enrollment and spanning 3 months also promotes retention through repeated contact via phone, text, or email according to the participant's preferred method of contact.

Additional strategies to promote retention and follow-up: Study participants will be asked to contact the study team if their phone number, address or PCP information changes between study visits; if needed, study staff may assist in re-establishing a primary care provider. The study team may collaborate with the participants PCP by contacting the PCP's clinic staff and/or sending an electronic message through the EHR to the PCP directly to inquire about the status of a patient for follow up on medication adherence, smoking status, or general issues regarding follow up participant contact information. For assessing abstinence, if the participant cannot complete the salivary cotinine test or remote CO monitoring and instead must come into the clinic for the CO breath test, we will make all efforts to coordinate with the patient during any pending appointments at VUMC so that they can take the CO test on a day when they are already scheduled to be at VUMC (e.g., study RA will travel to the One Hundred Oaks clinic or other VUMC clinics to meet participant).

6.0 Risks

The potential risks to subjects are not more than those of standard smoking cessation treatment. These include possible psychological distress from speaking with a counselor or answering questions about their smoking, discomfort or bruising from a blood draw, loss of confidentiality due to breach of protected health information, potential side effects of the process of quitting smoking, and potential side effects of smoking cessation medications, all of which are FDA-approved.

6.1 Smoking Cessation Medication Side Effects

In order to protect against potential risks associated with smoking cessation pharmacotherapy, this study involves FDA-approved medications according to label usage for smoking cessation aids. There is a risk of adverse side effects from FDA-approved smoking cessation medications, but this risk is not higher than that experienced by people taking the same medications outside of this research study.

The smoking cessation treatments in this study consist of counseling from trained tobacco treatment counselors in combination with safe and effective FDA-approved medications prescribed by the participants' inpatient team and/or PCPs. This combination of medication and counseling is the standard of care for smoking cessation treatment, and for those who successfully quit smoking, results in prolongation of life and improved quality of life.

Medication eligibility will be reviewed by two separate members of the study team (e.g., CTTS and PI or study coordinator and PI) to identify potential contraindications to nicotine replacement or varenicline.

- Nicotine replacement therapy (NRT): NRT is generally very safe, and several preparations have been sold over the counter for decades which is an indication of the FDA's view of their relative safety. The most common side effect of the patch is skin irritation or itching where the patch is applied, which is commonly managed by rotating patch sites and/or applying an OTC corticosteroid cream (such as 1% hydrocortisone). For nicotine lozenge/gum the most common side effects are mouth irritation, heartburn, hiccups. Many of the side effects of the lozenge/gum can be avoided by proper technique of the medication. For the nicotine inhaler and nasal spray, the most common side effects can include mouth/throat irritation, coughing, runny nose, watery eyes. In rare cases dizziness, headache, nausea, and rapid heartbeat can occur.
- Varenicline: Common side effects of varenicline include nausea and other gastrointestinal symptoms, sleep disturbance, and vivid dreams. The FDA-mandated EAGLES trial has established these medications as safe and effective. [52]
- Written and verbal instructions will be provided to patients to contact their PCP or the research study staff in case of adverse events that could possibly be medication-related. The IVR system (automated calls from approximately 3-days post hospital discharge (hospitalized patients) or 3-days post randomization (outside of hospital) to approximately 12 weeks post discharge or randomization, respectively) which helps protect participants by providing them with "on-demand' counseling designed to trouble-shoot any difficulties with study medication.

Advice for Participants

Participants may want to discontinue their medications due to possible side effects. Before medication is discontinued participants will be encouraged to adjust their

medication routine. For example, placing the patch on a different arm or place on the body and possibly even recommending a different brand of patch if allergic to latex or having a reaction to the adhesive. For oral NRT, patients will be reminded of proper usage of the product (gum, lozenge, inhaler, etc.) in order to avoid some of the most common and undesirable side effects.

For certain common side effects of FDA approved smoking cessation medication, such as mild-moderate gastrointestinal (GI) problems or mild-moderate sleep problems, study staff will provide the following advice:

- For moderate GI problems, study staff will remind the participant of proper administration (e.g., taking varenicline medication with food and water or milk) and reiterate that these side effects typically improve within 2-3 weeks after initiation of medication.
- For moderate sleep problems, study staff will remind participants of proper use (e.g., may remove patch at night or take the evening dose of varenicline earlier in the day or skip the evening dose, etc.) and will reiterate that the side effect typically improves within 2-3 weeks after initiation of medication
- Participants will also be reminded that many of these symptoms can accompany the process of quitting smoking *itself*, regardless of medication use.

For participants who normally drink caffeine or take caffeine pills, study staff will make the participant aware that chemicals (i.e., polyaromatic hydrocarbons) in cigarette smoke metabolize/break-down caffeine, so generally smokers "need" more caffeine when they are smoking at their usual rate. However, as smoking is reduced or stopped altogether, caffeine levels may rise, causing a person to feel jittery, irritable, nauseated, etc. Participants may be instructed to reduce caffeine intake by half, and thereafter to adjust caffeine intake to comfort.

6.2 Venous Blood Draw

This is a routine procedure that is considered standard of care in clinical medicine. For participants who consent to provide a genetic sample in addition to the NMR, we will attempt to collect a single blood sample of approximately 15 ml (3 teaspoons) at the bedside or at an outpatient lab by clinical phlebotomy/study staff. This blood will be utilized for the enrollment consented NMR test and future genetic analysis. Blood for genetics will be discarded if a participant does not consent to genetics. The blood draw will be performed by trained personnel using universal precautions to protect both the participant and personnel. The risks to subjects are minimal, but may include pain, allergic reaction, infection, or bleeding at the needle stick site. These usually resolve without any specific medical therapy over the course of minutes to days.

6.3 Nicotine Metabolite Ratio (NMR) and Salivary Cotinine Testing

There are no known serious adverse effects from these tests. Nicotine metabolites (ratio of 3-hydroxycotinine to cotinine) will not be clinically reported beyond the study (i.e., NMR results only given to hospital team and provided to the PCP as described above).

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

7.1 Specification of Adverse Events

An **Adverse Event (AE)** is defined as any untoward or unfavorable medical occurrence or undesirable experience associated with the use of a medical product in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with participation in the research, whether or not it is considered related to participation in the research. AEs are graded as follows:

- Mild (no limitation of usual activities),
- Moderate (some limitation of usual activities), or
- Severe (inability to carry out usual activities)

AEs will be attributed according to the relationship to the study drug and/or procedure as:

- Unknown,
- Unrelated related,
- Possibly related,
- Related

An AE can therefore be any new sign, reaction, symptom, event, disease or a worsening in frequency or severity of a preexisting condition that occurs during the course of the study. Stable chronic conditions that were present prior to study entry and do not worsen are not considered AEs. An event is considered "related" if it is likely to have resulted from participation in the research study and is considered "unanticipated" when it was unforeseeable at the time of its occurrence. An **unanticipated problem (UP) involving risk to participants or others** is "Any event that was (1) unanticipated, (2) related, and (3) places participants or others at a greater risk of physical or psychological harm than was previously known or recognized."

A **serious adverse event** is defined as any adverse event that results in any of the following outcomes:

- Death
- life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization

- persistent or significant disability/incapacity
- congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse event is defined as any adverse event, the specificity or severity of which is not consistent with the risk information described in the general investigational plan.

Suspected Adverse Drug Reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suspect a causal relationship. It is considered unexpected if it is not consistent with the risk information described in the general investigational plan. A suspected adverse drug reaction will be defined as a recorded adverse event that is unexpected and deemed to be possibly, probably, or definitely related to the study drug.

7.2 Methods and Time for Assessing, Recording, and Analyzing Safety Parameters

Participant health status will be assessed during the baseline survey to document any chronic conditions or symptoms that existed prior to the study. This list will be reviewed and compared to reported events throughout the study. If the participant reports the same symptom, occurring at the same severity, during subsequent visits, the symptom should not be recorded as an Adverse Event (AE). However, if the event is new (not previously reported) or the severity has worsened, as determined by RA, then the AE should be reported.

In the case of unresolved AEs, study staff will update the AE log if they become aware of follow-up information.

All AEs will be assessed to determine if they meet criteria for a Serious Adverse Event (SAE). If the AE is serious, then appropriate reporting measures will be followed (see section 7.5). Investigators will consult with the IRB or NIH, if uncertain how to classify an event.

7.3 Procedures for Eliciting Reports of and for Recording and Reporting Adverse Events

Medical conditions/pre-existing conditions (Table 3) and medical symptoms (Table 4) will be assessed at baseline. Medical symptoms will be assessed at follow up timepoints. All events, including changes in severity of any of the below mentioned medical symptoms, will be documented in a study database.

Table 3: Medical Condition/Pre-existing Conditions Checklist

Medical Condition/Pre-existing Conditions Checklist	
A	Anemia or "low blood"
B	Congestive Heart Failure, also called weak heart or fluid on the lungs
C	Dementia or "Alzheimer's"
D	Diabetes or high blood sugar or "sugar"
E	Liver Disease or a bad liver or Cirrhosis
F	Chronic Hepatitis B
G	Chronic Hepatitis C
H	High cholesterol, lipids, or triglycerides
I	Hypertension or high blood pressure
J	Pancreatitis
K	Bad nerves in your feet causing pain and numbness (neuropathy)
L	Bad circulation in your legs or feet
M	Chronic lung disease (emphysema, asthma, chronic bronchitis or chronic obstructive lung disease)
N	Kidney Failure (or bad kidneys)
O	Stroke or "mini" stroke (Transient Ischemic Attack)
P	Pneumonia
Q	Shingles
R	TB or Tuberculosis
S	Post-Traumatic Stress Disorder
T	Schizophrenia (hearing voices or seeing things that others don't)/schizoaffective disorder
U	Depression (depressive disorder)
V	Anxiety (anxiety disorder)
W	Bipolar Disorder
X	Any kind of Cancer (please list type below) 1._____ 2._____ 3._____ 4._____ 5._____

Y	Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS)

Table 4: Medical Symptoms

Medical Symptoms	No	**Yes→**Date of the symptom(s)and severity of the symptom(s) (mild, moderate, severe)
A. Agitation and/or Irritability		
B. Anger and/or hostility		
C. Depressed mood		
D. Anxiety (includes nervousness and panic attacks)		
E. Restlessness		
F. Insomnia		
G. Abnormal dreams and/or nightmares		
H. Headaches		
I. Dizziness		
J. Nausea and/or vomiting		
K. Abdominal Pain		
L. Fatigue		
M. Hiccups		
M. Cough		
O. Mouth/Throat Irritation		
P. Skin irritation		
Q. Heartburn		

7.4 Adverse Event (AE) Reporting

All adverse events (AE) and unanticipated problems (UP) will be reported to the IRB by the study team within the mandated time frames. Ultimately, the PI and study coordinator will review any serious adverse events and report them to the IRB and NIH.

The PI will report AE and UP to the VUMC IRB in accordance with IRB policies:

- Required reporting to the IRB within 7 calendar days of the Investigator's knowledge of the problem which includes serious adverse events, injuries, side effects, deaths, or other problems occurring at VU, VUMC or other locations in which the Investigator is responsible for the conduct of the research and the VUMC IRB serves as the IRB of Record:
    - Any serious AE that in the Investigator's opinion was unanticipated or unexpected, involved risk to participants or

others and was at least possibly related to the research procedures; and/or
    - Any noncompliance with the IRB-approved protocol that increased risk or affected the participant's rights, safety, or welfare.

- Any UP listed above requires reporting to the IRB even after the participant has completed the study or after the participant has withdrawn from the study including after study closure.

7.5 Data Safety and Monitoring Board

The Data and Safety Monitoring Board (DSMB) will monitor the MIST trial. The DSMB will act in an advisory capacity to the study PIs to monitor participant safety, data quality and evaluate the progress of the studies being conducted.

The DSMB is responsible for ensuring subject safety (by reviewing blinded and unblinded safety data on a regular basis and assessing the safety of study procedures) and for monitoring the overall conduct of the studies. The DSMB will monitor enrollment, follow up and adverse events.

The DSMB is an independent group advisory to the PI and study team, and is required to provide recommendations about conduct of the trial. In addition, the DSMB is asked to make recommendations, as appropriate, about:

- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Protocol violations and adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Participant safety
- Notification of and referral for abnormal findings

The DSMB will consist of 3 members and strong consideration will be given to include at least one investigator with expertise in smoking cessation, 1 statistician, and 1 investigator with expertise in clinical trials. The DSMB will meet twice during the course of the study, which will be scheduled after approximately one third and approximately two thirds of the target number of participants have reached the final outcome. The DSMB has the authority to assess the option of stopping early for overwhelming benefit demonstrated in the primary study endpoint, or for safety concerns. The panel will make recommendations about the continuation, modification, or termination of the study to the study steering committee. Unscheduled meetings can be requested by any party with the responsibility of overseeing the study.

8.0 Study Withdrawal/Discontinuation

Study withdrawal: A participant can voluntarily withdraw from the study at any point in time throughout the course of the study. The participant will not be penalized in any way for voluntarily withdrawing from the study. To withdraw, the patient will be asked to inform the research team in writing of their intent to withdraw including their reason for leaving the study. Participants who withdraw from the study will no longer be eligible for compensation for any study procedure that was not completed prior to withdrawal. If, during the enrollment and randomization process, or shortly thereafter, it comes to the attention of the study staff that a participant has become ineligible (e.g., patient's medical condition deteriorates while in hospital such that they are now too ill to participate; patient develops a medical condition that makes them ineligible to use smoking cessation medication, etc.), then the team would cease the enrollment process and/or administratively withdraw the participant.

Medication discontinuation: Participants who choose on their own to discontinue medication may do so. Other conditions may prompt study staff to recommend medication discontinuation. For example, pregnancy and lactation are exclusion criteria for the study. If during the study a participant informs study staff of a pregnancy, the participant will be asked to discontinue study medication and to visit the PCP for a confirmatory pregnancy test. Other conditions that would prompt study staff to recommend discontinuation of medication include side effects that could not be managed with usual good clinical practice. All participants who discontinue their medication for any reason will be followed and analyzed by intention to treat.

9.0 Statistical Considerations

9.1 Aim 1

The primary study outcome is biochemically-verified self-reported 7-day point prevalence abstinence at 6 months as defined by salivary cotinine level < 10 ng/ml or expired CO <10 ppm. A secondary outcome is biochemically-verified self-reported 7-day point prevalence abstinence at 12 months. Brief surveys will be conducted at 6 and 12 months after study enrollment to determine self-reported abstinence. Biochemical validation of smoking status is accomplished via mailed salivary cotinine samples or expired CO.

Analysis:
The effect of MIST vs. UC on biochemically-verified abstinence at 6 months will be estimated via a relative risk of abstinence and tested at a 5% significance level via a chi-squared test with Yates' continuity correction. The same method will be applied

to the secondary outcome at 12 months. Anticipated loss to follow up is accounted for in the expected approximate UC abstinence rates where persons lost to follow up will be treated as non-abstinent. However, sensitivity analyses will consider a range of possible odds ratios (1, 2, and 5) linking loss to follow-up and smoking. [51] Exploratory analyses testing for effect heterogeneity will use multivariate logistic regression models adjusting for the main effect of a potential modifier and testing for an interaction with the effect of MIST. The potential effect modifiers to be explored are age, race, sex, NMR, and pre-intervention plan to quit.

Power:
Conservatively assuming a biochemically validated abstinence rate of 10% under UC, a chi-squared test on 1000 patients (at 6 months) will detect a MIST abstinence rate of 16.2% (Risk Difference=6.2%, Relative Risk=1.62, Odds Ratio=1.74) with 80% power. Assuming a 15% biochemically validated abstinence rate under UC (at 12 months), a 22.2% rate under MIST (RD=7.2%, RR=1.48, OR=1.62) is detectable with 80% power. Power was estimated via simulating 20K datasets under the settings above in the statistical program R and were checked against the simplified estimates of the pwr package.

9.2 Aim 2

A secondary outcome is participant self-reported medication adherence assessed at the 1- and 3-month surveys (Aim 2a). Another secondary outcome is PCP prescriptions for smoking cessation medication after study enrollment for participants who continue to smoke. Pharmacy data from CMS will also be used to supplement participant's self-report of whether they received smoking cessation medication prescriptions from their PCP after study enrollment (Aim 2b) and whether the prescriptions were matched to NMR (Aim 2c).

Analysis:
To account for the longitudinal structure of the data with observations at months 1, 3, 6, and 12, Aim 2 analyses will utilize general estimating equations (GEE) with an autoregressive (AR1) correlation structure adjusting for self-reported smoking status and age, race/ethnicity, education, and dependence (baseline FTND score) in a multivariate logistic GEE model. Each of the following three models will estimate a common odds ratio for MIST vs UC for the outcome of interest. All patients will be included in the analyses and missing covariate data will be multiply imputed via predictive mean matching imputation. Standard errors will be estimated via Rubin's rules and statistical significance tested via Wald tests. Unobserved adherence status or prescriptions will be treated as non-adherent or not received, respectively. H2a: We will estimate the odds ratio for being adherent in the 3 months post-enrollment. H2b: We will estimate the odds ratio for receiving a PCP prescription for a smoking cessation medication in the 12 months post-enrollment. PCP prescriptions occurring between any two time points, e.g. months 3 and 6, will be attributed to the latter time point for analysis. H2c: We will estimate the odds ratio for receiving an NMR-

matching PCP prescription. Exploratory and sensitivity analyses: For each of the three outcomes, exploratory analyses will test for interactions between the MIST effect and month of follow up; and for interactions between the MIST effect and medication type (NRT or varenicline). Sensitivity analyses will vary the correlation structure assumptions to ensure the main conclusions are robust to model specifications.

Power:
For all hypotheses related to clinical implementation, we conservatively estimate power by focusing on the first observation time point. Under a common odds ratio, power will be higher when analyzing all time points together. H2a: Assuming a self-reported adherence rate of 50% under UC, analysis of 1000 patients (at 3 months) will detect a MIST adherence rate of 59.0% (Risk Difference=9.0%, Relative Risk=1.18, Odds Ratio=1.44) with 80% power. H2b: Because self-reported abstinence at a given time point will be a very strong predictor of not receiving a PCP prescription for smoking cessation medication at the following time point, with regard to statistical power the sample sizes will be effectively reduced by the respective quit rates. For this effective sample size reduction, we conservatively assume quit rates of 15% for UC and 25% for MIST. Assuming a PCP prescription rate of 30% under UC, a 39.8% rate under MIST (RD=9.8%, RR=1.33, OR=1.54) is detectable with 80% power. H2c: Similarly, assuming an NMR-matching PCP prescription rate of 15% under UC, a 23.2% rate under MIST (RD=8.2%, RR=1.55, OR=1.71) is detectable with 80% power. Power was estimated via simulating 20K datasets under the settings above in the statistical program R and were checked against the simplified estimates of the pwr package.

9.3 Aim 3

Passive surveillance of 12-month clinical composite outcomes (ER visit, hospitalization, or death) in VUMC and non-VUMC facilities is also conducted by specific members of the research team.

Analysis:
The effect of MIST vs UC on the Aim 3 primary outcome of a healthcare composite outcome consisting of hospitalization, emergency department visit, and/or death within 12 months will be estimated via a relative risk of the composite outcome and tested at a 5% significance level via a Chi-squared test with Yates' continuity correction. The same method will be applied to the secondary outcomes of hospitalization, ED visit, and mortality analyzed separately. Exploratory analyses testing for effect heterogeneity will use multivariate logistic regression models adjusting for the main effect of a potential modifier and testing for an interaction with the effect of MIST. The same modifiers as in Aim 1 will be tested. All analyses will be reported as primary, secondary, or exploratory as specified here.

Power:

The composite health care and mortality outcomes are gathered via VUMC EHR, state vital records, and the existing Tennessee HDDS, thus patients are presumed to not have an event unless one is observed. Conservatively assuming a composite outcome rate of 50% under UC (which is based on EHR estimates from VUMC smokers in care), a Chi-squared test will detect a MIST rate of 41.0% (RD=-9.0%, RR=0.82, OR=0.70) with 80% power. Assuming rates for UC of 10%, 20%, and 30% respectively for mortality, ED visits, and hospitalizations, a Chi-squared test on 1000 patients will detect with 80% power MIST rates of, respectively, 5.1%, 13.2%, and 22.0% (RD=-4.9%, -6.8%, 8.0%; RR=0.51, 0.66, 0.73; OR=0.48, 0.61, 0.66).

10.0 Privacy/Confidentiality

10.1 Data Collection and Retention

All study data will be captured electronically and stored via a secure, web-based data capture system, REDCap and an Access database. Paper forms will be used during enrollment, if needed, and stored securely in a locked cabinet that only study staff will have the ability to access. Records will be kept indefinitely but will be destroyed if no longer needed.

10.2 Quality Control Process

Quality control measures for capturing data: Study databases will include detailed specifications for completion of data, including rules for question skip logic, built-in validation rules for error checks, as well as computer algorithms to check for out-of-range codes and internal inconsistencies. Study staff will be trained in methods for responsible and complete data collection. All data, regardless of capture method, will be reviewed for logic, skip patterns, response ranges, out-of-range codes, and internal inconsistencies, and converted to SAS (or equivalent statistical package) datasets for analysis.

Call back quality assurance: Study tobacco treatment counselors/coaches will have dedicated, protocolized training in tobacco treatment. A subset of calls will be monitored by the study coordinator and/or Principal Investigator (PI) for quality assurance.

10.3 Data Security and Confidentiality

To prevent the loss of data, all electronic information is stored within the VUMC firewall and is password-protected. If there are any hard-copy, original consent forms and other study documents including participant names and contact information will be kept in binders and locked in a filing cabinet. Electronic participant data will be placed into a password-protected, web-based database on

encrypted computers and iPads by study personnel. Electronic medical records, and electronic participant tracking spreadsheets will be stored on a secure server. Only the research staff, the study PI and co-investigators will have access to this data. Data quality (including visits completed during intervention window, data missingness, and recruitment rates) will be monitored monthly by the database manager and systematic data problems will be reported to the PI.

A unique identification number will be used to protect the confidentiality of the study participants. This number will be assigned at the time of study enrollment. Only the investigator, coinvestigators and research personnel will have access to the key and information that identifies participants as being in this study. Digital data files will be coded so that the participant name or other such identifiers are not in the filename. Participants will be asked to complete a Release of Information, giving study staff permission to share study-related information with each participant's primary care provider via phone, mail, fax, email.

All procedures are in accordance with best practices for Federal Health IT as determined by the Office of the National Coordinator for Health Information Technology (ONC). Protected health information will not be exchanged outside of the approved study personnel at VUMC.

Data Security and Confidentiality - TelASK
The informed consent document will state clearly to patients that the study is being done as a collaboration between VUMC and TelASK, a company that makes automated phone calls. Subjects will be informed that in order to make the phone calls, TelASK will be given information such as their name, study ID, phone number, sex, preference for time of call, and the date that they are discharged from the hospital or enrolled. During the study, TelASK will establish a secure website to view call results in real time, quit status, and "on-demand" counseling requests. Data will be transferred to TelASK via HIPAA-compliant secure FTP. This plan is consistent with what the VUMC IRB has approved for our ongoing NIH funded study of hospitalized smokers (5R01HL11182107: PIs Rigotti and Tindle). Upon completion of the study, data will be transmitted back to VUMC's secure password-protected computer system. All patient data will be purged from TelASK's data files.

Data Security and Confidentiality – Samples
Blood samples used for NMR will be collected and labeled using information such as the study participant number, and/or MRN and stored in a secure location until NMR analysis is conducted by Vanderbilt Pathology Laboratory Services (VPLS), ARUP (currently contracts with VUMC) or other equivalent laboratory.

Blood or saliva for future analyses of genetics and other potentially relevant biological markers will be collected, de-identified, and stored in a secure location, in the laboratory of Dr. Quinn Wells in Light Hall.

Salivary cotinine/CO samples collected for biochemical validation of self reported abstinence will be labelled with study participant number.

Table 1: Survey and Abstracted Electronic Health Record Data

Construct	Measures	Source	Baseline timepoint (CSF, RASF, Baseline survey)	1 m	3 m	6 m	12 m
Sociodemographic Factors	Age, sex, education, race/ethnicity, employment, living situation, health insurance type	Patient	X				
Medical Condition/Pre-existing Conditions Checklist	**Pre-existing condition** – VACS [53]; WHI Extension Study, HIV/AIDS [54] (Coronary heart disease, chronic obstructive pulmonary disease, stroke, cancer, hypertension, diabetes, hyperlipidemia)	Patient/ EHR/Proxy	X				
	Pregnancy		X	X	X	X	X
	COVID-19 (infection status, amount smoked, influence on quit attempt)		X				
Medical Symptom Screening	**Adverse Events**	Patient/ EHR/Proxy	X	X	X	X	X
Tobacco Related Variables	**Nicotine dependence** Fagerstrom Test of Nicotine Dependence (FTND) [55]	Patient/ Proxy	X				
	Tobacco use Baseline: cigarettes per day, years smoked, other tobacco use Follow-up: duration of abstinence after enrollment, cigarette and other tobacco product use in the past 7 days		X	X	X	X	X
	Electronic cigarette use Baseline: use in the past 30 days, frequency of use [56] Follow-up: use since enrollment, in past 7 days		X	X	X	X	X
	Smoking in home Rules for smoking in home [39]		X			X	
	Smoking cessation beliefs Confidence in ability to quit (10-point Likert scale) [57]		X	X	X	X	X
	Quit attempt		X	X	X	X	X

	Definition: intentional tobacco abstinence lasting >24 hours. Baseline: past year Follow-up: since enrollment or since last follow-up contact						
	Tobacco cessation treatment Definition: FDA-approved cessation medications, behavioral support (telephone quit line, text-message support, in-person counseling, internet programs, mobile phone applications), other Baseline: Prior use Follow-up: Use since enrollment or since last follow-up contact, adherence	Patient/ Proxy	X	X	X	X	X
	Medication Satisfaction Treatment Satisfaction Questionnaire for Medication (TSQM) (version 1.4)[58]					X	X
	Social support for quitting smoking Number of people available for support. [59]	Patient	X				
Other Substance Use	**Alcohol use** Alcohol Use Disorders Identification Test (AUDIT-C), heavy drinking-*only on follow ups*[60, 61]	Patient/ EHR/Proxy	X	X	X	X	X
	Drug use Marijuana, cocaine, opioids, stimulants, drugs by injection (Veterans Aging Cohort Study -VACS, *modified*)[61]	Patient/ Proxy	X			X	X
Psychological Factors and Quality of Life	**Depression and anxiety symptoms** Patient Health Questionnaire (PHQ-4) [41]	Patient/ EHR/Proxy	X	X	X	X	X
	Resiliency Brief Resilience Scale (BRS) [63]	Patient/ Proxy	X				
	Optimism/pessimism Life Orientation Test (LOT-R) [45]		X			X	X
	Quality of life		X	X		X	X

	Baseline, Follow up months 6/12: Medical Outcomes Study - Short Form (SF-1) [64], quality of life (EQ-5D-5L) [64] Follow-up month 1: SF-1 only						
	Delay discounting Task 5 Trial Delay Discounting [46-48]		X				
Risk Assessment	**Objective Risks of Lung Cancer, CHD** • **Tammemagi Risk Calculator:** includes age [numeric, years], race [pick 1], smoking status [current/former/never], CPD [numeric], years smoked [numeric], COPD/emphysema/chronic bronchitis [Y/N], personal hx **any** cancer [Y/N], family hx lung cancer [Y/N], BMI [weight in kg/height in meters^2]) [65]	Patient/ EHR	X				
	• **Framingham Risk Score** for Coronary Heart Disease (includes age [numeric, years, range 30-79], sex [M/F], smoking status [Y/N], Total Cholesterol [numeric, mg/dL or mmol/L, max 1000], HDL cholesterol [numeric, mg/dL or mmol/L, max 150], Systolic BP [numeric, mm Hg, max 300], Blood pressure being treated with meds [Y/N]) [66, 67]		X				
	Perceived Health Risk Risk of smoking, benefit of quitting (5-point Likert scales) [44]	Patient	X				
Healthcare Related Variables	**Hospital course** Length of hospital stay, discharge diagnosis	EHR	X				
	Post-enrollment care coordination PCP visit, discussion of tobacco cessation treatment	Patient/ Proxy		X	X	X	X
	Health care utilization Post-enrollment ED visits, hospital re-admission (items from the National Health Interview Survey)	Patient/ EHR, state, federal		X	X	X	X

		DB/Proxy					
Program Feedback	**<u>Services provided by the study</u>** Automated phone calls, counselor contact feedback	Patient/ Proxy		X	X	X	X

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