Comparing Smoking Cessation Interventions among Underserved Patients Referred for Lung Cancer Screening: A Randomized Clinical Trial

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Protocol Summary

Title	Comparing Smoking Cessation Interventions among Underserved Patients Referred for Lung Cancer Screening
Short Title	pRCT of smoking cessation interventions among underserved patients
Principal Investigator	Scott D. Halpern, MD, PhD
Co-Investigators	*University of Pennsylvania:* Anil Vachani, MD, MS; Kevin Volpp, MD, PhD; Joanna Hart, MD, MS; Dylan Small, PhD; Alisa Stephens-Shields, PhD; Rachel Kohn, MD, MS; *Kaiser Permanente Southern California:* Michael Gould, MD, MS; Mohamed Ismail, MD MPH; *Geisinger Health System:* Matthew Facktor, MD; Charlotte Collins, PhD; *Henry Ford Health System*: Christine Neslund-Dudas, PhD; Michael Simoff, MD; *SUNY Buffalo:* Leonard Epstein, PhD
Design	Pragmatic randomized clinical trial
Objectives	To compare the effectiveness of four interventions to promote sustained, biochemically confirmed smoking abstinence for 6 months among underserved smokers referred for lung cancer screening at four large U.S. health systems.
Trial Duration	4 years
Study Sites	The University of Pennsylvania Health System including Lancaster General Hospital; Henry Ford Health System; Geisinger Health System; Kaiser Permanente Southern California
Sample Size	3,200 patients
Patient Eligibility	1) Age ≥ 18 years 2) Current smoker (≥ 1 cigarettes per day, not including e-cigarettes) 3) Has a low-dose computed tomography (LDCT) scan ordered by his or her physician 4) Able to receive study invitation and screening, by virtue of showing up to a radiology location affiliated with participating health systems for the LDCT, or having a valid email address or telephone number on file with the health system 5) Underserved, defined as one or more of the following: i. Black ii. Hispanic iii. Rural residence iv. Low socioeconomic status, defined as one or both of: a. ≤ high-school education or less b. household income < 200% of the federal poverty line 6) Access to a phone with text messaging or the internet

Interventions	Patients will be individually randomized into 4 arms: 1. Basic usual care: Ask-Advise-Refer (AAR) approach 2. Enhanced usual care: usual care plus free nicotine replacement therapy and reduced-cost FDA-approved pharmacotherapies 3. Enhanced usual care plus financial incentives to stop smoking 4. Enhanced usual care plus financial incentives plus a mobile health application that motivates patients to think about their future health by promoting episodic future thinking (EFT)
Outcomes	**Primary Outcome:** Biochemically confirmed smoking abstinence that is sustained for 6 months. **Secondary Outcomes:** Secondary smoking-related outcomes include point-prevalent quit rates at 2 weeks and 3 months, and relapse rates at 12 months. Secondary patient-reported outcomes include: • Motivation to quit • Self-efficacy related to cessation efforts • Perceived barriers to cessation • Temporal discounting • Health-related quality of life
Analysis of Primary Outcome	• Intention-to-treat approach, such that all patients meeting eligibility criteria who are randomized will be evaluated as assigned
Study Oversight	• A Stakeholder Advisory Committee comprising patients, representatives from community and policy organizations, and clinician and payer leaders will advise the investigators about study implementation, including through the review of patient-facing materials and by helping to mitigate any unforeseen risks or burdens that may arise. • Trial oversight will be conducted by the University of Pennsylvania (Penn) Institutional Review Board (IRB00009947) as the central IRB of record, with reliance agreements executed with participating health systems' IRBs. • A Data and Safety Monitoring Board (DSMB) will be convened to review the trial protocol, address any safety concerns that may arise, and make recommendations regarding trial continuation, modification, or termination.

Contents

1. Abstract

Low-dose computed tomography (LDCT) screening reduces mortality among current and former smokers at high risk for lung cancer, and is widely recommended by national guidelines. LDCT also increases access to care and thus provides an opportunity to deliver smoking cessation interventions to current smokers in conjunction with this screening. As the burdens of smoking are greatest, and the effectiveness of standard interventions lowest, among patients who are black, Hispanic, from rural residences, and/or are less educated or have lower incomes, such underserved patients are at high risk for poor smoking-associated health outcomes. Correspondingly, they may stand to benefit preferentially from smoking cessation interventions delivered in conjunction with LDCT. However, it is unknown which interventions best promote cessation in the screening context. By comparing standard with incrementally more intensive interventions, this trial among 3,200 current smokers in four health systems will address the uncertainty health systems face regarding how best to help high-risk smokers quit.

2. Background and Rationale

Stopping smoking greatly reduces morbidity and mortality among patients eligible for lung cancer screening**.** Cigarettes remain the leading cause of preventable morbidity and mortality worldwide,[1,2] causing at least 5 million deaths annually, including half a million in the U.S.[2-4] The National Lung Screening Trial found that annually screening current and former heavy (at least 30 pack-years) smokers aged 55-75 using low-dose computed tomography (LDCT) reduces mortality.[5] Thus, annual LDCT screening is widely recommended by national guidelines.[6,7,8] Because more than 5 million Americans who are eligible for LDCT are current smokers,[9-10] and in light of evidence that smokers who quit while undergoing screening gain an average of 4 years of life expectancy due to reductions in lung cancer and other tobacco-related illnesses,[11-13] national guidelines recommend,[6, 14, 15] and the Centers for Medicare and Medicaid Services (CMS) requires,[16-17] that smoking cessation interventions be delivered as core components of LDCT screening programs. To successfully reduce harm from tobacco and promote cessation goals, we aim to expand the armamentarium of evidence-based strategies for smoking cessation. We propose conducting a 4-arm pragmatic randomized clinical trial among current smokers who are referred for lung cancer screening.

While there is limited evidence regarding the comparative effectiveness of different ways to promote smoking cessation, few studies have examined cessation strategies among underserved populations. Research suggests that embedding smoking cessation interventions within LDCT screening programs may be particularly beneficial for underserved patients because screening produces an extra clinical contact,[18-19] and because the burdens of smoking-related illnesses are greatest among patients who are black, Hispanic, and/or have low socioeconomic status (SES).[20-23] Enrollment in this study has been targeted towards racial minorities, ethnic minorities, low-income groups, and residents of rural areas to identify unique needs of this patient population in order to help them find their best support related to smoking cessation.

The approach currently used by most U.S. lung cancer screening sites is "Ask-Advise-Refer," whereby patients are asked if they smoke, advised of the benefits of cessation, and referred to local cessation resources including behavioral counseling.[24, 25] However, the overwhelming majority of patients exposed to this approach continue smoking.[26] The other commonly used approach is to provide free nicotine replacement therapy (NRT) and the two FDA-approved medicines for smoking cessation (varenicline and bupropion). Despite the wide adoption of pharmacotherapy interventions among health care systems in the US, this strategy also lacks evidence of effectiveness as part of LDCT screening. In a recent pragmatic trial in workplace settings, PI Halpern found that providing free access to cessation aids failed to promote cessation.[27] In contrast, financial incentives have been shown to be effective in improving health in a variety of areas, including smoking cessation. In the two largest smoking cessation trials, financial incentives totaling $600-800 were found to triple sustained smoking cessation rates compared with usual care groups 6 months after quitting.[27-28] Following a period of 6 months where incentives were discontinued, these differences between groups remained intact, supporting the use of incentives for sustainable cessation efforts.

Given the limited evidence regarding how best to promote smoking cessation in the context of LDCT screening programs, both the NIH[29] and National Academy of Medicine[15] have highlighted the need to identify more effective smoking cessation programs. Smokers tend to be "present-biased" with a propensity to discount future benefits (e.g., greater health following smoking cessation) in favor of immediate satisfactions (e.g. the pleasures of smoking). By contrast, cancer screening is an event that naturally motivates people to adopt a future orientation,[30] or state of prospection,[31] as they contemplate how their future lives may differ based on whether they receive reassuring or concerning results. This may explain why patients undergoing screening express increased motivation to quit smoking.[18,32] Thus, screening programs represent a prime setting within which to deploy a mobile health application, "Episodic Future Thinking" (EFT), that helps people imagine futures selves that are healthier and/or wealthier by virtue of having quit (and thus, having saved the money they would have spent on cigarettes). This study will also assess whether EFT may work in a complementary fashion to financial incentives – with incentives providing an immediate, extrinsic motivation to quit, and EFT helping to sustain abstinence by enhancing people's intrinsic motivations to be healthier and wealthier in the long term.

3. Objectives

3.1. Specific Aims

Our primary objective is to help underserved patients who are referred for lung cancer screening to quit smoking. We will complete three specific aims:

1. Compare the effectiveness of the two main interventions currently used to promote smoking cessation in the context of lung cancer screening:
   (i) Ask-Advise-Refer, and
   (ii) Ask-Advise-Refer plus free access to nicotine replacement therapy and reduced-cost FDA-approved pharmacologic cessation aids

2. Compare these standard approaches with multicomponent interventions that add one or both of:
   (iii) Financial incentives for successfully quitting, and
   (iv) Financial incentives plus a mobile health application that motivates patients to think about their future health through episodic future thinking.
3. Assess heterogeneity in the effectiveness of these four interventions in promoting cessation among smokers that differ by age, race, ethnicity, income, financial wellbeing, education, rurality, tobacco dependence, internet access, comorbid illnesses, and objectively reported and patient-perceived lung cancer screening results.

3.2. Primary Outcome

The primary outcome measure is sustained abstinence for 6 months, and will require self-report of smoking cessation followed by biochemical confirmation at 2 weeks, 3, and 6 months.

3.3. Secondary Outcomes

Secondary smoking-related outcomes include:

- Point-prevalent quit rates at 2 weeks and 3 months, and relapse rates at 12 months

Secondary patient-reported outcomes (PROs), include:

- Motivation to quit
- Self-efficacy related to cessation efforts
- Perceived barriers to cessation
- Temporal discounting
- Health-related quality of life

See §7.6. Baseline Survey and §7.9.2. Biochemical Testing for additional information on methods and study instruments used to measure outcomes for the trial.

4. Study Design

4.1. Overview

We will conduct a 4-arm randomized trial comparing these 4 interventions to promote sustained, biochemically confirmed smoking abstinence for 6 months among smokers in underserved demographic groups. The 3,200 participants to be enrolled will be current smokers who are black, Hispanic, and/or have low socioeconomic status (defined as household income <200% of the federal poverty line or a high school education or less) or rural residence who are referred for LDCT screening at 4 large health systems. Patients with LDCT orders will be identified via the electronic health record and further screened for eligibility. Eligible patients will enroll and complete the study using the NIH-funded *Way to Health* portal.

The primary outcome will be biochemically confirmed, sustained abstinence from smoking tobacco for 6 months following participants' selected quit dates. We will conduct intention-to-treat analyses using logistic regression to compare the overall effectiveness of the interventions among all randomized

participants. Because not all participants will engage with their assigned intervention in this pragmatic design with opt-out consent, we will also conduct secondary analyses to compare the specific efficacy of interventions, conditional on acceptance. This approach entails a two-stage residual inclusion model in which the randomization to the treatment components is used as an instrumental variable in causal odds ratio treatment effect analysis. We will also compare effectiveness among patients who differ in terms of age, race, ethnicity, income, financial wellbeing, education, rurality, degree of tobacco dependence, internet access, comorbid illnesses, and the results of their LDCT screens (concerning vs. reassuring results), testing for statistical interaction between these factors and treatment assignment to guide future targeting of optimal interventions for individual patients.

4.2. Study Setting

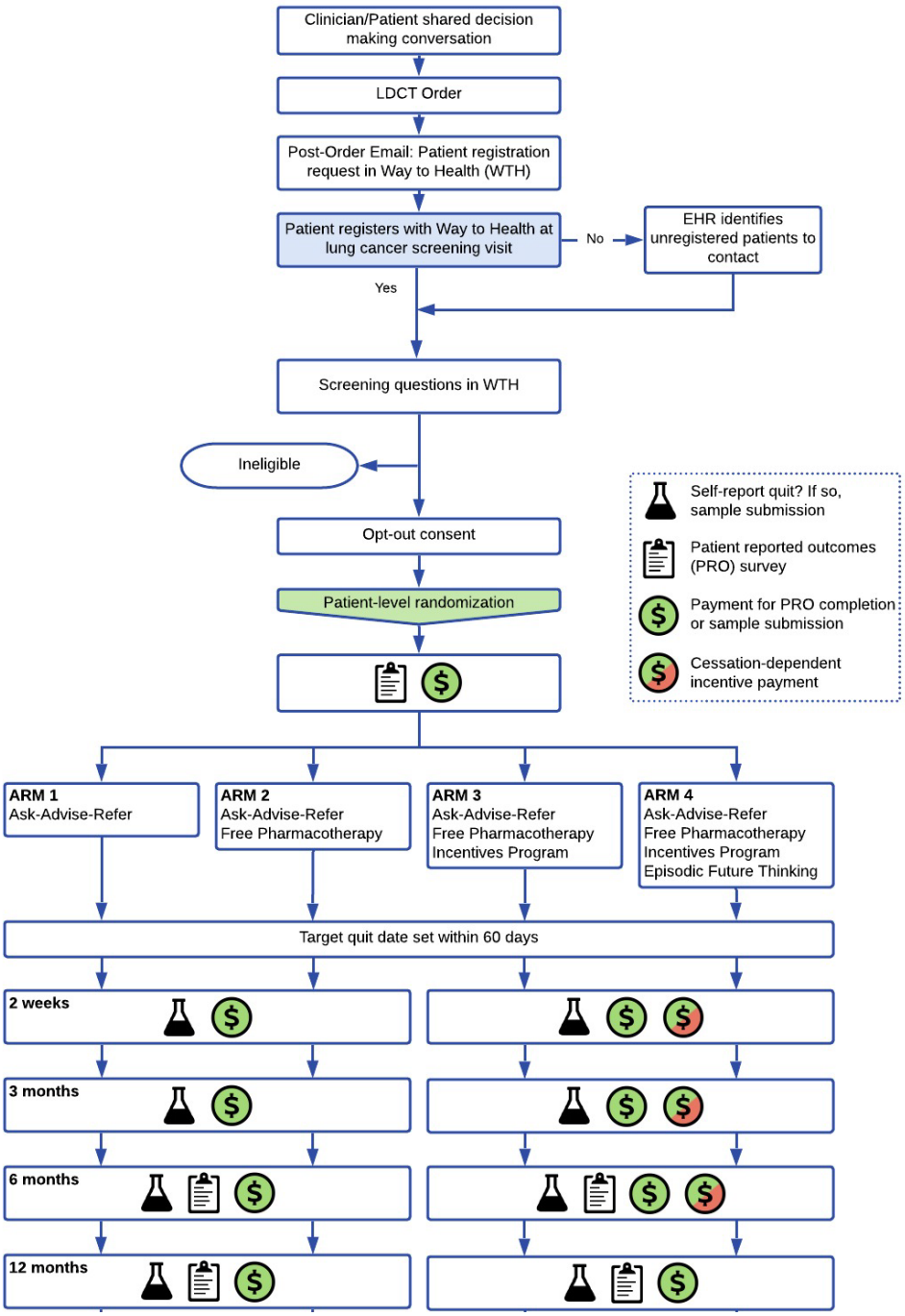
We will test the interventions during the course of providing usual care among underserved patients who have been referred for lung cancer screening in the outpatient setting within four health systems: University of Pennsylvania Health System (Penn), Geisinger Health System (Geisinger), Kaiser Permanente Southern California (Kaiser), and Henry Ford Health System (Henry Ford). These health systems were purposefully chosen as each serves a core constituent of our underserved patient groups. Kaiser is an integrated health system in Southern California that serves many Hispanic patients, as well as those who are black and low-SES. Geisinger serves patients who are predominantly from rural residences in Pennsylvania, and roughly half are low-SES. Henry Ford serves patients in the Detroit Metro area, where approximately 35% of patients are black and/or of low SES. Serving the Philadelphia Metro area, nearly half of the Penn's patients are black, and many are low-SES.

Reflecting the real-world nature of this pragmatic trial, all recruitment outreach efforts will be conducted either by non-study health system personnel who facilitate LDCT screening in outpatient settings, or via electronic outreach facilitated by REDCap. There are no on-the-ground research staff within the outpatient settings of each health system.

4.3. Schema

This is a prospective randomized controlled trial with longitudinal follow-up of patients over 12 months.

Figure 1. Study Schema



5. Subject Recruitment

5.1. Accrual and Duration

Accrual will proceed over 32 months, beginning at the University of Pennsylvania and followed by the

other three health systems. We expect to accrue 3,200 patients over a 32-month period; however, the clinical trial will proceed over a 42-month period, to account for the longitudinal follow-up of enrolled patients of up to 12 months. Based on historical data provided by the participating health systems regarding LDCT appointments among our target population, we anticipate a projected enrollment rate of 107 patients/month. We expect our highest accruing sites will be (in descending order): Kaiser, Penn, Geisinger, and Henry Ford.

All enrolled patients will be contacted for a minimum of 12 months to complete 12-month surveys.

5.2. Inclusion Criteria

All of the following patient inclusion criteria must be met:

1) Age ≥ 18 years
2) Current smoker (≥ 1 cigarettes per day, not including e-cigarettes)
3) Has a low-dose computed tomography (LDCT) scan ordered by his or her physician
4) Able to receive study invitation and screening, by virtue of showing up to a radiology location affiliated with participating health systems for the LDCT, or having a valid telephone number on file with the health system
5) Underserved, defined as one or more of the following:
    v. Black
    vi. Hispanic
    vii. Rural residence
    viii. Low socioeconomic status, defined as one or both of:
        a. ≤ high-school education or less
        b. household income < 200% of the federal poverty line
6) Access to a phone with text messaging or the internet

It is expected that LDCT orders will be placed by physicians in line with national screening guidelines, i.e., in 2019, guidance recommended LDCT scans for patients aged ≥ 55 years with a ≥ 30 pack-year smoking history and tobacco use within the past 15 years. National screening guidelines drafted in 2020 propose lowering the age criteria to ≥ 50 years with a ≥ 20 pack-year smoking history and tobacco use within the past 15 years. Although the majority of enrolled patients in the clinical trial are expected to be ≥ 50 years, patients < 50 years meeting all other eligibility criteria are eligible for this clinical trial.

5.3. Participant Remuneration

The 12-month maximal payment schedule for surveys, sample collections, and financial incentives is given below. All enrolled participants will be asked to complete 6-month and 12-month surveys, regardless of their self-reported abstinence status. Only invited patients are allowed to participate in activities and eligible to earn money. Participants are only required to submit biochemical samples if they first self-report continued abstinence at the 2 week, 3-, 6-, and 12-month time points (see §7.9. Longitudinal Assessments). If participants are assigned to Arms 2-4 and choose to pursue pharmacotherapy prescriptions from their physicians for varenicline or bupropion, they will additionally be able to submit for reimbursement on the *Way to Health* website for filled prescriptions up to a total dollar amount of $300. If patients are assigned to Arms 3 or 4, they will additionally be eligible to

receive up to $600 in financial incentives contingent on their continued biologically-confirmed abstinence at 2 week, 3-, and 6-month time points.

Participants in Arm 1 are eligible to receive a maximal payment amount for surveys, short assessments, and sample collection of $420. Participants in Arm 2 are eligible for the same maximal payment amount for surveys, short assessments, and sample collection, plus up to $300 in reimbursement of out-of-pocket expenses for prescription smoking-cessation medications, for a total possible remuneration of $720. Participants in Arm 3 are eligible for the same maximal payment amount for surveys, short assessments, and sample collection, plus up to $300 in reimbursement of out-of-pocket expenses for prescription smoking-cessation medications and up to $600 as incentives for cessation, for a total possible remuneration of $1,320. Participants in Arm 4 can additionally receive $20 as compensation for engaging with the intervention and setting their personalized EFT cues, bringing their maximum remuneration to a total of $1,340. Participants in Arms 3 and 4 who receives $600 or more in compensation in a calendar year will be asked to report their Social Security Number in *Way to Health* to complete a W9 and be sent a 1099 for tax reporting purposes. Please note that payments for activities associated with the "12-month" time-point contribute toward the annual $600 threshold for the second year due to lags associated with assessing quit status and survey completion and payment processing. As such, no participant in Arm 2 will reach the $600 annual threshold in any given year.

Please note that if patients in Arm 1 respond that they have <u>not</u> quit smoking at 2 weeks (or 14 days later as part of a second chance opportunity) they will receive a maximal payment amount of $130 for completion of surveys and two short assessments. If patients in Arms 2-3 respond that they have not quit smoking at 2 weeks (and again at 1 month as part of a second chance opportunity) they will receive a maximal payment amount of $430 for completion of surveys, two short assessments, and prescription medication reimbursement. Patients in Arm 4 who respond that they have not quit smoking will receive a maximal payment amount of $450 for completion of surveys, short assessments, prescription medication reimbursement, and setting EFT cues. Based on prior studies, the majority of participants will receive less than $600 annually because they either do not quit smoking, quit smoking then relapse, and/or do not order prescription medications.

Time Period	*Maximum Remuneration Amount*					
	Surveys	*Short Assessments*	*Biochemical Samples*	*Prescription medication reimbursement (Arms 2,3, and 4)*	*Incentives (Arms 3 and 4 only)*	*EFT (Arm 4 only)*
Baseline	$40			$300 [f]		$20 [h]
Quit date		$0				
2 weeks		$5	$45 [c, d]			
Second chance		$5 [a]	$45 [c, d]		$100	
3 months		$5 [b]	$45 [c, d]		$200 [g]	
6 months	$40	$5 [b]	$45 [c, d]		$300 [g]	
12 months	$40	$5 [b]	$95 [c, e]			
Total	**$120**	**$25**	**$275**	**$300**	**$600**	**$20**

Notes:
[a] *Second chance assessment is contingent on patient-self report of smoking continuance*
[b] *Short assessment survey is contingent on biochemically confirmed abstinence at previous time-point*
[c] *Biochemical sample is contingent on self-reported quit status in the short assessment for that time-point*
[d] *Samples collected at a lab are reimbursed $45 and samples collected at home are reimbursed $15*
[e] *Samples collected at a lab are reimbursed $95 and samples collected at home are reimbursed $35*
[f] *Participants may submit for reimbursement for out-of-pocket expenses for prescription medications up to $300*
[g] *Opportunity for incentive payment is contingent on biochemically confirmed abstinence at previous time-point (i.e., incentive payments are only for sustained abstinence)*
[h] *Remuneration is contingent on completing FutureMe activity*

Patients will receive payments through issuance of GreenPhire ClinCards that will be mailed to participants after completion of the baseline survey. These ClinCards can be used in the same manner as a reloadable debit card. ClinCards can be re-loaded remotely with additional funds by study team members via the *Way to Health* platform after completion of longitudinal study activities.

6. Randomization

6.1. Groups

We plan to compare the effectiveness of four interventions, as follows:

Arm 1: Usual care

Participants randomized to this basic usual care arm will receive the usual care approach, Ask-Advise-Refer, which is a standard approach in which clinicians ask smokers about their desire to quit smoking, advise them to quit, and provide informational resources such as hotlines, specialized clinics, or smoking cessation classes.

Arm 2: Enhanced usual care

Participants randomized to this arm will receive the usual care of Ask-Advise-Refer as well as access to reduced-cost prescription medications (varenicline/Chantix or bupropion/Zyban) and free nicotine replacement therapy (NRT). Health systems are increasingly adopting this approach of offering these smoking cessation aids for free to similar patients.

Arm 3: Enhanced usual care plus financial incentives

Participants in this arm will receive all aspects of enhanced usual care plus an incentive plan in which they will be informed of their eligibility to earn $100, $200, and $300 if they submit negative tests for nicotine metabolites at 2 weeks, 3 month and 6 months following the quit date, respectively.

Arm 4: Enhanced usual care plus financial incentives plus a mobile health application

Participants in this arm will receive all aspects of Arm 3 plus an intervention, FutureMe, to promote episodic future thinking (EFT). EFT has been shown to reliably reduce discounting of the future. Patients will practice using FutureMe cues to envision the “future is now” between the time of enrollment and

the quit date, and will then receive cues from the quit date through the end of the intervention period, 6 months later, unless they ask to stop receiving cues sooner.

6.2. Assignment

Participants will be randomized individually, stratified by health system, to 1 of the 4 arms using random number generation within the *Way to Health* platform. At the Penn, Geisinger, and Henry Ford sites, 25% of enrolled participants will be assigned to each of the 4 arms. Participants enrolled at Kaiser sites will only be assigned to Arms 2-4, each with a 33% probability. This is because Kaiser provides free cessation aids to all patients, and as such, there exists no basic usual care (control) arm (for this reason, participants recruited through Kaiser must also be a member of Kaiser Permanente). Based on the expected accrual at each of the four health systems, we expect that overall there will be 470 participants in basic usual care (Arm 1), and 910 participants in each of intervention arms 2-4.

7. Study Procedures

7.1. Eligibility Screening

All four health systems use the same EHR platform, EPIC, resulting in programming efficiencies for data extraction. At all health systems, placement of a LDCT order signifies that a patient has had tobacco use within the past 15 years. The presence of a LDCT order among adult patients will be the only EHR criterion to flag approach to complete secondary eligibility questions related to smoking status (i.e., to assess if a current smoker) and demographics (i.e., to assess their underserved status), as described in §7.2. Smokers can qualify for the study on the basis of race, ethnicity, rurality, or socio-economic status (SES). Although some demographic attributes (e.g., race, ethnicity) can be assessed somewhat reliably on the basis of EHR-based data, smoking status is under-captured within the EHR, SES cannot be reliably assessed without patient self-report of their education level and household income, and self-reported rurality requires patient self-report.

There are considerable logistical advantages to approaching all adult patients presenting for LDCT screenings. Specifically, this approach does not require health system staff to differentiate between eligible and ineligible patients in order to proceed with enrollment, but rather can be embedded into the routine operational workflow at the LDCT screening sites. We will permit patients ≥ 18 years with a LDCT order to participate in the trial given that some integrated health systems like Kaiser allow LDCT orders to be placed for patients < 55 years (and reimburse accordingly) and draft national guidelines have recommended lowering the minimum age to 50 years. We anticipate that approaching all adult patients during lung cancer screening will result in recruitment of some patients in the 50-55 age range, but believe that this will connect more underserved patients who are at risk for lung cancer with interventions that could help them quit smoking.

7.2. Recruitment

Consistent with the goals of a large, scalable, pragmatic clinical trial, there are no research personnel on site to recruit patients. Instead, patients will be approached by non-study health system personnel

during their lung cancer screening visit (either at a dedicated lung cancer screening clinic or a radiology site). Health system personnel will give an iPad tablet to all adult patients referred for a LDCT scan as part of either their admissions process or transfer to the LDCT scanner. For ease of embedding in the clinic workflow, the iPad will be given to all adult patients and not just smokers. At Henry Ford, the lung cancer screening staff will introduce the program as part of their joint decision making session for patients undergoing their first LDCT scan, and let patients know to expect a follow-up communications (texts and/or emails) from the Healthy Lung program. Patients undergoing annual scans will receive text messages ahead of their radiology appointments.

We will supplement our recruitment outreach efforts with text-based and email-based outreach at all health systems, with touchpoints at time of LDCT order, at time of the LDCT appointment, and two touchpoints within 10 days of their appointment. These additional outreach efforts are especially important recruitment adjuncts during the ongoing COVID-19 pandemic. This text-based approach will adhere to best practices in texting, such as allowing users to reply STOP if they don't want to be contacted again. A similar primary approach of text-based outreach will be undertaken at Henry Ford Health System, but only targeting those who are identified as smokers.

We will have a bilingual hotline staffed by two University of Pennsylvania staff to answer any questions patients might have during the enrollment process. However, we also anticipate that patients may have questions of the frontline staff with whom they interact. Accordingly, we propose that clinic leadership receive training and communication materials ahead of trial launch covering such aspects as: (a) Administration (e.g., charging and locking up iPads), (b) A high-level description of the study goals, study design, the online research platform *Way to Health*, study approvals, and study contacts, (c) An information sheet with anticipated questions and answers from patients such as anticipated timelines, how to create an account on the online research platform, and the bilingual hotline to call if they have any questions about the program or the online research platform. Clinic staff will be blinded to interventions assigned to individual participants through the online research platform, unless a patient volunteers to tell them. Staff are not involved in any other aspects of the longitudinal study and thereby cannot influence study outcomes. We will ask clinic staff to direct questions to our hotline wherever possible.

In situations where the patients are given an iPad but have insufficient time to finish registration and enrollment during their lung cancer screening visit, patients will automatically be sent reminder emails and text messages, with a reminder phone call if there is no patient response to those reminders. Each health system will build automatic processes for extracting EPIC data to identify patients who have lung cancer screening orders but never scheduled a LDCT appointment within 120 days or who presented for their lung cancer screening appointment but did not register in *Way to Health*. This latter situation could happen in instances where the participants were called back to the CT scanner before being given an iPad by the staff. In these instances, staff within each health system will be responsible for contacting patients by email, mail, text, and/or phone to provide them with an additional opportunity and encouragement to enroll.

7.3. *Way to Health* Registration

Way to Health is a comprehensive online research platform developed by the University of Pennsylvania that will be deployed for this study. *Way to Health* links a web-based participant portal to a variety of peripheral devices (including cell phones) for assessing health behaviors; provides an infrastructure for communicating with and providing feedback to patients by email or text message at patients' discretion; mediates electronic transfer of payments for study tasks or incentives for smoking cessation; delivers mobile health applications, such as EFT; and administers surveys.

The *Way to Health* platform for this study will be accessible in both English and Spanish. The email invitation and iPads will have easy-to-follow instructions for registering in *Way to Health* and patients will also be given information about a hotline to call for English or Spanish assistance with navigating through the website. After registration in *Way to Health*, patients will be asked whether they are a current smoker (smoke ≥ 1 cigarettes per day; not including e-cigarettes), and additional eligibility criteria related to race, ethnicity, income, education, rural residency, and cell phone access. Patients who smoke but do not fall into one of the underserved categories, will be provided with information about local resources to help them quit smoking.

After registration and eligibility confirmation in *Way to Health*, patients will be given further information about the four steps that will happen next as part of their program enrollment: (1) completing a survey – for which they will be paid $40, (2) learning about tools available to them to help them quit smoking, (3) setting a goal for the date that they wish to quit smoking, and (4) getting paid for taking the short assessment. Patients will then be presented with opt-out language, which includes study details and optional FAQs about study participation. As the study was approved with use of an opt-out consent process within theW2H portal, patients who are identified as eligible and who chose to review the program FAQ's are presented with the option to decline participation by calling or sending an email to the study team. However, due to the technological limitation of the W2H platform, we were not able to design this process to be fully consistent with an opt-out model. Under a true opt-out model, those who do not actively decline would be automatically enrolled. However, the platform requires one extra step for patients to be enrolled – they have to click a "continue" button to proceed. The consequences of this technological inflexibility allow for patients to get "stuck" – that is, they have neither declined participation nor clicked the "continue" button. A root-cause analysis of this revealed that some patients did not click continue because, although they were interested in the program being offered, they were not ready to quit smoking at that time. This represents a scientific problem, as this is a pragmatic trial specifically designed to test the real-world effectiveness of interventions being offered to ALL smokers who identify with one or more underserved populations and who have an order for a lung cancer screen. It was explicitly designed to overcome limitations of nearly all other smoking cessation trials that only accrue patients who are "ready" to quit. To address this, those who are "stuck" will be messaged within a few weeks and informed that this is their last chance to opt-out, and again reminded that they can do so by emailing or calling the study team. Patients will then have 3 days from receiving the message to contact our team to decline participation; otherwise, research staff will manually advance these patients to be enrolled. The manual approach is necessitated merely due to a technological

limitation in the W2H platform that prevents true opt-out consent from being actualized. Participants are informed during enrollment that they may withdraw permission to use and disclose their information at any time, including after the study ends. After randomization, participants are then directed to complete a baseline survey and view the *Way to Health* patient portal to read about information specific to their randomization arm (see §7.8).

7.4. Waivers of Consent and HIPAA Authorization

We will seek approval from the University of Pennsylvania (Penn) IRB, as the central IRB of record, to conduct the trial using an opt-out consent process. This approach is known as a *waiver or alteration of the requirement for individual informed consent* and is advocated for pragmatic trials testing methods for comparing and improving the delivery of established interventions within health care systems.[33-36] Recent NIH-funded research by our group and others reveals that patients generally endorse opt-out consent or simple notification approaches in pragmatic trials when such mechanisms help achieve the goals of the study.[37-39] Although large-scale, pragmatic, comparative effectiveness trials have previously been undertaken without consent at all, including by PI Halpern,[40] both our investigative team and our study's Stakeholder Advisory Committee strongly advocated for an opt-out consent process for this underserved population. Directly following eligibility screening, eligible participants will receive messaging in *Way to Health* about this voluntary program, will be directed to further information, and given the opportunity to easily opt-out.

Below we describe the many reasons why an opt-out enrollment is appropriate for this trial.

- **Minimal Risk:** The risks to subjects of participating in this comparative effectiveness study are minimal. The interventions being tested are available outside of the research study, and are aimed at improving patient's health by helping them quit smoking, which has numerous benefits to health. Indeed, the only foreseeable study-related risk is a breach of confidentially.
- **Impact on Subjects Rights and Welfare:** The waiver will not adversely affect the rights and welfare of patients because they will receive information both prior to, and directly after, randomization about what is involved in the program. Patients will be informed that the care that they receive will not be affected if they decline the program. All materials on the *Way to Health* platform will be in Spanish and English and use plain language and adopt culturally competent messaging strategies.
- **Waiver Essential to Research:** An opt-out design is essential to answer the questions we are interested in: what rates of sustained smoking abstinence might health systems achieve if they actually rolled out the interventions to be tested among all their patients who are referred for lung cancer screening who are actively smoking, and how do these interventions compare in terms of their effectiveness? This population of all patients referred for lung cancer screening who currently smoke is precisely the population of interest for health systems because they are required, as a condition of Medicare reimbursement for lung cancer screening, to offer smoking cessation interventions to all patients who smoke at the time of that screening. There is no real-world setting in which the interventions would only be made available to those patients who have screening ordered, currently smoke, AND have an interest in quitting and would opt in to participate in a research study.

Yet that is the sample that would be obtained if we did not use an opt-out consent model, whereby patients are engaged with the program unless they actively choose otherwise. As programs similar to the current trial are being developed and disseminated across the country, it is imperative that we examine how these interventions perform across diverse health systems using their full eligible patient populations, lest these systems will make care decisions based on flawed information from highly selected patient samples. Furthermore, employing a waiver of consent for this trial will help to connect high-risk smokers to potentially helpful treatments that they may not otherwise seek out.

Although the foregoing discussion of how opt-out consent is the only way in which we can answer the research question is the most important reason by that approach is essential, there are also logistical considerations. Due to the large sample size needed for this study it would be impractical to employ study staff to manually recruit and consent 3,200 participants across more than 60 clinics in multiple health systems. Traditional recruitment, outreach, and consent by study staff for this trial would exhaust all of our financial and labor resources, as well as significantly lengthen the time needed to conduct this trial. It would be impractical to conduct this study in the traditional manner. Using an opt-out approach will allow this research to be conducted in a more time- and cost-efficient manner.

- **Additional Information to Subjects:** The Common Rule suggests that, to the extent possible, the subjects will be provided with pertinent information after participating in the trial. In line with this recommendation we will further notify all patients about the results of the study prior to publication. Investigators and Stakeholder Advisory Committee (SAC) members will partner to host webinars for study participants. These will allow participants to view and listen to presentations of key findings and participate in an interactive question-and-answer session. Those without internet connection will be able to listen in and ask questions via regular phone. SAC members representing community organizations and health system-based wellness programs will also hold in-person town halls exclusively for study participants to learn and discuss the study findings. SAC member and communications expert George Fernandez from Latino Connection will facilitate webinars and town halls for Spanish-speaking study participants. Investigators and SAC members will prepare a public report summarizing the study design and results in both Spanish and English. This report will be distributed by mail and email, and will be posted online. We will partner with SAC members to ensure the report uses culturally competent messaging strategies about smoking cessation and lung cancer screening resources relevant to study participants and contact information for study staff and SAC members. This communication will be submitted to the IRB for approval following that vetting process but prior to sending it to any study participants.

Employing a waiver of consent for this trial will help to connect high-risk smokers to potentially helpful treatments that they may not otherwise seek out. Enrolling large numbers of smokers in a study in which all will be offered some form of assistance with cessation provides high expected benefits, both to enrolled participants and in terms of the knowledge to be gained. While smoking rates have reduced to 18% in the United States, smoking related illness still remains the leading cause of preventable death in the United States. More than 75% of current American smokers wish to quit; 45% do quit for at least a

day each year; and anti-smoking policies, new pharmaceuticals, and behavioral modification programs offer promise to help them. Nevertheless, only 2-3% of smokers attain prolonged abstinence annually. Given this high interest in quitting smoking, and low rates of successfully sustaining quit attempts with currently available programs, opt-out consent will ensure that all smokers will have the same access to potentially helpful programs. Findings of the study will be published, and if successful, this trial could serve as a model for health systems across the country to implement similar programs.

This clinical trial meets the three criteria for a waiver of HIPAA authorization in accordance with the provisions for using protected health information (PHI) set forth in 45 CFR 46, § 164.512 (i) as follows: (1) the researchers require access to protected health information (PHI) in order to conduct the research, (2) the research cannot be practicably conducted without the waiver, and (3) the use or disclosure of PHI poses no more than minimal risk to participants. However, given that the study already furnishes opt-out consent language to patients as part of the enrollment process, the University of Pennsylvania IRB recommended that the HIPAA Authorization language be bundled in with this opt-out consent language.

7.5. Allocation

Participants will be randomized in the *Way to Health* platform to one of the four study arms, as described in §6.2., at which point patients are considered assigned to the Intention-to-Treat (ITT) analyses.

7.6. Baseline Survey

Participants are asked to complete a baseline survey assessing the following:

- Nicotine dependence. *The Fagerström Test for Nicotine Dependence (FTND) is a widely used and validated 6-item measure to assess the intensity of physical addiction.*
- Motivation to quit. *The Stages of Change (SOC) is a validated 1-item measure to assess patient's self-reported motivation to quit.*
- Self-efficacy related to cessation efforts. *We will use the 10-item situational measure of self-efficacy to measure patients' self-efficacy to quit smoking.*
- Perceived barriers to cessation. *The Challenges to Stopping Smoking Scale (CSS-21) is a validated 21-item measure to assess patients' perceived barriers to smoking cessation. The CSS-21 has two sub-scales: intrinsic factors (physical, psychological or cognitive aspects of quitting) and extrinsic factors (social or environmental aspects of quitting).*
- Lung cancer screening. *Participants will be asked whether they have received their lung cancer screening results and if anyone in their household has a history of lung cancer or currently smokes.*
- Smoking history. *Smoking history will be assessed for number of years of smoking, quit attempts, pack-history, and use of nicotine replacement therapies, e-cigarettes, or other tobacco products.*
- Financial wellbeing. *The Consumer Financial Protection Bureau (CFPB) abbreviated financial wellbeing scale is a 5-item scale that assesses control, capacity to absorb a shock, being on track to meet goals, and freedom of choice..*
- Health-related quality of life. *The EuroQuol Group's EQ-5D scale is a 25-item validated scale used*

to assess patients' perceived health-related quality of life across the domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

- Temporal (or "delay") discounting. *We will use a 5-item, adjusting-delay task developed by Co-I Epstein and colleagues.*

7.7. Setting a Quit Date

Participants are asked to set a target quit date (TQD) within the next 60 days. If no TQD is selected, a default TQD will be set at 60 days with email and/or text message reminders sent weekly for up to 6 weeks (or less dependent on local health system practices) to remind participants to select their own personalized target quit date. We have set a window of 60 days so that participants have sufficient time to obtain free cessation aids on *Way to Health* (Arms 2-4) or develop and practice EFT cues on *Way to Health* (Arm 4) before their TQD. Participants will receive email and/or text-message reminders at 14, 7, and 1 day prior to their TQD to alert them of the date they selected. Each participant's TQD will then become their "day 0" – the point from which all subsequent study dates and endpoints in this study will be measured. A short quit date assessment survey will be given at the TQD to assess smoking status. A short assessment aimed at determining smoking status will be given at 2 weeks and those who report having successfully quit will be asked to undergo a urine cotinine and anabasine test (see sections §7.9.1. and §7.9.2.). Patients who self-report that they are still smoking at 2 weeks post TQD will be given the opportunity to return to "day 0" and have one additional chance to document abstinence 2 weeks later.

7.8. Intervention Assignment

Participants are directed on the *Way to Health* platform to information specific to their randomization arm. Between enrollment and the quit date, patients may obtain free cessation aids (arms 2-4), receive financial incentives (arms 3 and 4), and develop and practice cues for use in the EFT intervention (arm 4), as detailed below.

7.8.1. Ask-Advise-Refer

On the *Way to Health* platform, participants will be able to view standard information such as the national quit hotline and local health system resources (e.g., Penn's smoking cessation clinic) and will be informed that they will be sent emails and/or texts at quit date, 2 weeks, 3 months, and 6 months to assess cessation status. Patients will be advised to speak with their own clinician about any other available local resources. We conceive that information on *Way to Health* will act to reinforce any Ask-Advise-Refer information already given to participants when their physicians placed the LDCT order.

7.8.2. Cessation Aids

Monthly supplies of NRT products can be ordered directly, free of charge, through *Way to Health* and distributed via mail by a NRT distributor (e.g., Ebix). Participants can choose to select either patches, gums, or lozenges, with a combination patch/gum or combination patch/lozenge pack set as the default recommended option. NRT product usage and dosage will be available at the time of ordering and also provided in mailed materials. Once selected, all shipping charges will be paid by the study. Participants are informed that they can seek a prescription from their own physician for two FDA-approved

pharmacotherapies, varenicline and bupropion. Participants who choose to pursue pharmacotherapy prescriptions from their physicians for varenicline or bupropion will be able to submit for reimbursement on the *Way to Health* website for filled prescriptions up to a total dollar amount of $300. Cessation aids will be available to all participants up until the time of the Quit Date assessment (or second chance assessment), after which time cessation aids are only available to those participants who maintain their quit status up to 6-months from their quit date.

Since Kaiser offers free NRT to all their patients, participants enrolled at Kaiser are not given this benefit through the program. However, early analysis showed that Kaiser participants were reporting less use of NRT than participants enrolled under Arms 2-4 at the other health systems. To address this, the program was modified in the Fall of 2022 to message Kaiser participants about accessing NRT through their health system and to aid in that process. The messaging frequency was developed to mirror how NRT is offered through Healthy Lungs at the other participating health systems.

7.8.3. Financial Incentives

Participants will be informed of an incentive plan for successfully quitting and maintaining abstinence over six months. Participants will be informed of their eligibility to earn $100, $200, and $300 if they submit negative tests for nicotine metabolites at 2 weeks, 3 months, and 6 months following their target quit date, respectively. Participants will be informed of the need for biochemical testing to be eligible to receive payments (see §7.9.2). Participants will receive payments through deposition of additional funds directly onto their GreenPhire ClinCard, which they received in the mail after completion of the initial baseline survey.

7.8.4. Episodic Future Thinking

Participants will have the option of watching two short bilingual FutureMe videos on the *Way to Health* patient portal that will help guide them through the process of developing personalized “cues” that can be accessed over the next six months. Content will describe EFT and how it’s thought to work and specifics on how to generate good EFT cues. Online content in the patient portal will address commonly cited barriers to accessing and using cues. Between the time of enrollment and the quit date, participants will practice generating their own EFT cues to envision the “future is now”, by writing out positive, vivid descriptions of events that they’re looking forward to in the future. All participants are instructed to imagine and describe in detail events that are positive, specific, and vivid. Participants are prompted to describe specific details of their events, including who was there, what was happening, where the event took place, and how they felt. Participants are instructed to describe the events as though they were currently happening. Over the intervention period, *Way to Health* will then regularly prompt participants by text with their pre-specified EFT cues to envision a future, healthier self that has achieved his or her goal of quitting smoking. Participants will receive cues on a pre-determined schedule as well as on-demand from the quit date through the end of the intervention period, six months later, unless they ask to stop receiving cues sooner.

7.9. Longitudinal Assessments

This is a longitudinal study whereby participants will repeatedly be asked to complete (i) smoking status updates, (ii) sample submissions, and (iii) patient-reported outcomes (PRO) surveys. During the

enrollment process, participants will indicate on their profile whether they prefer to be contacted by the study team by text message, email, or both modalities. Participants will then receive a notification via text message and/or email when they are required to complete one of these activities at a given time point. Each text message or email will include a link to the *Way to Health* website as well as information about what activity they need to complete. When a participant logs onto the website, a notification on the homepage will prompt him or her to complete the appropriate survey or link them to instructions on how to complete a sample submission.

7.9.1. Smoking Status Updates

Short assessments aimed at determining smoking status will be emailed and/or texted to participants at 2 weeks, 3 months, 6 months, and 12 months. Assessments will take < 2 minutes to complete and will assess the use of cigarettes, other tobacco products, NRT, and e-cigarettes. Assessments can be completed via a link to the *Way to Health* platform. Those who achieve abstinence at a given time point will continue to be queried regarding their abstinence at the next time point and invited to submit samples if they continue to self-report abstinence.

7.9.2. Biochemical Testing

To assess sustained smoking abstinence at 2 weeks, 3 months, 6 months, and 12 months, we require biochemical confirmation following self-report of abstinence. Those who self-report abstinence in the short assessments will be given instructions on the *Way to Health* platform about their nearest available testing facility. Once the lab order is placed, participants will then be instructed to have their abstinence confirmed biochemically within 14 days (within a 28-day window to enter test results) and provided information regarding remuneration. As a pragmatic trial, we recognize that there may be situations where the participant is unable to complete the lab within the parameters and will allow for flexibility. Participants will also be told whether they need to complete a urine cotinine, urine anabasine, or serum carboxyhemoglobin test, dependent on whether or not they are currently using any NRTs or e-cigarettes, as below:

> *Urinary cotinine test:* for participants not reporting the use of NRT. A urinary sample with cotinine < or equal to 50 ng/ml will be used to confirm cessation.
>
> *Urinary anabasine test:* for participants reporting use of NRT, as cotinine tests cannot distinguish cigarette nicotine from replacement therapy nicotine. A urinary sample with anabasine < 3 ng/ml will be used to confirm cessation.
>
> *Serum carboxyhemoglobin test:* for participants only using e-cigarettes and no other tobacco products who self-report quitting. A blood carboxyhemoglobin level of < or equal to 4% will be used to confirm cessation.

Due to the location of the participants in this trial and the difficulty for some more remote or elderly patients to come in for testing we will offer sample submission in two different ways. Participants will be encouraged to submit samples for biochemical confirmation of abstinence at their health system's labs or local Quest labs using instructions from *Way to Health*; however, we will also allow patients to arrange through *Way to Health* to submit samples using a mobile collection agency, ExamOne. ExamOne

is a Quest diagnostics company that collects samples in patients' homes and sends those samples to Quest Diagnostics for processing. Those participants who achieve biochemically confirmed abstinence at 2 weeks will continue to be invited to submit biochemical samples at 3 months, 6 months, and 12 months, if they continue to self-report abstinence. If a person self-reports a relapse at a given time point, they will not be invited to submit samples at subsequent time-points. If: 1) lab results are outside the threshold of our parameters for confirmed cessation and the participant contacts the study team shortly after being notified of the results to question the accuracy of results, and 2) the Second Chance option is not available, then the participant may be allowed to retest.

Participants will be informed that they will be reimbursed differential amounts for submitting the sample at home or at a lab, according to the fee structure below:

Biochemical test	Health System/Quest Lab		ExamOne Mobile Service	
	2 weeks 3 months 6 months	12 months	2 weeks 3 months 6 months	12 months
Urinary cotinine	$45	$95	$15	$35
Urinary anabasine	$45	$95	$15	$35
Serum carboxyhemoglobin	$45	$95	$15	$35

7.9.3. Patient-Reported Outcomes (PRO) surveys

Participants will be asked to complete PRO surveys at 6 months and 12 months analogous to the baseline survey, excluding demographic questions. These surveys will ask about participants' self-reported motivation to quit, self-efficacy related to cessation efforts, perceived barriers to cessation, health-related quality of life, and temporal discounting.

8. Data Management

8.1 Data Collection

All research data for enrolled patients will be captured electronically via the EHR and the NIH-supported *Way to Health* web platform (RC2-AG036592). All four health systems using the same EHR platform, EPIC, resulting in programming efficiencies for data extraction. *Way to Health* (https://www.waytohealth.org/) is an integrated, cloud-based platform that will substantially increase the efficiency of patient enrollment and tracking, data management, and financial disbursements. By trial launch, all *Way to Health* online pages will be available in Spanish as well as English. Additionally, we will use REDCap databases to conduct outreach to potentially eligible patients, by text and/or email. Each health system will house their own REDCap outreach database to ensure that information on potentially eligible patients is restricted to their own HIPAA entity.

8.2 Data Management

At the University of Pennsylvania there are senior staff from the Palliative and Advanced Illness Research (PAIR) Center and the Center for Health Incentives and Behavioral Economics (CHIBE)'s *Way to Health* team to establish and monitor all data management protocols. Senior *Way to Health* personnel provide

managerial infrastructure specifically designed to provide all of the data management services. This research study is also staffed by a research support team at each of the four health systems, namely a project manager and a data manager and/or programmer. These study personnel at Geisinger, Kaiser, Henry Ford and Lancaster General Hospital (within the Penn system but on a different instance of EPIC EHR) will have direct data access to *Way to Health* study data submitted by patients within their own respective health systems. Data access groups will be set up in *Way to Health* that restrict study team members at other health systems from accessing PHI of patients outside their own health system. As the prime site, the Penn study staff (project managers, data managers, hotline staff) will have access to all contact information of patients registered in *Way to Health* from across the four health systems in order to coordinate study activities (e.g., delivery of cessation aids, reimbursements for prescription medications, order lab tests in the Quest Quanum eLabs portal, emails and two-way texts via Twillio to study participants according to the study schedule, and study payments). Access to all the study data will be limited to specifically designated researchers who are responsible for contacting participants for follow-ups and responding to questions and concerns from participants. All research staff accessing *Way to Health* complete a Data Security Agreement upon initial login to the platform.

Patients' register their name and contact information (email, phone, mailing address) on the HIPAA-compliant *Way to Health* website so that they can be contacted longitudinally (see § 7.9 Longitudinal Assessments). All patient-reported responses to surveys and assessments will be linked to each participant by a unique *Way to Health* user ID number.

Patients order monthly supplies of NRT products on the *Way to Health* platform, but the products are distributed via mail by a NRT fulfilment company. The University of Pennsylvania will disclose names, mailing address, and product details to the NRT fulfilment company for the sole purpose of the delivery of products ordered by the patient, and will communicate this to patients as part of the online ordering process. Participants in Arms 3 and 4 may be requested to submit their social security number if they are to receive payments above the cumulative annual threshold of $600. Social security numbers will be securely entered into in *Way to Health* and Greenphire and transmitted in encrypted format to University of Pennsylvania's Accounts Payable, which will store the data for W-9 forms and be sent a 1099 for tax reporting purposes.

Patients who self-report smoking cessation will submit biochemical samples for collection and testing at health system labs, Quest labs, or via ExamOne mobile service. The University of Pennsylvania will disclose name, gender, date of birth, and *Way to Healt*h ID (the minimum required elements) through the Quanum portal to Quest Diagnostics and ExamOne for the sole purpose of creating a lab order for the patient, and will communicate this to patients as part of the online process for selecting a lab site. Biochemical test results will be integrated into *Way to Health* using unique patient identifiers. Lab results for Quest and ExamOne will be available to Penn staff through the secure Quanum e-portal for integration into *Way to Health.* Lab results from the health system labs at Geisinger and Henry Ford will be uploaded directly by health system staff into the *Way to Health* platform.

Way to Health study data will be linked to additional health information emanating from the health systems' EHRs, including objective screening results, prescriptions for smoking cessation medications (e.g. Rx written, filled, refilled), presence of high burden of chronic comorbid illnesses, presence of certain mental health diagnoses, number of prior LDCT scans, and other data elements required to calculate a Tammemagi lung cancer risk score (e.g., BMI). Patient identifiers such as name, DOB, and date of screening visit will be used to accomplish the EHR linkage through flexible matching in a programming script ("R" script, or equivalent). At Penn, this linkage will be undertaken by Penn study team members. At the other three health systems, this linkage will be undertaken by the study team members (programmers and project manager) at their respective institutions. At intervals requested by the DSMB, and at the end of the study, these study team members will create "limited datasets" that will then be securely transferred via a secure file transfer protocol (sFTP) from the other three health systems to Penn and stored on secure servers by the PAIR Center data manager(s) (see §8.4. Data Security).

8.3. Data Monitoring

The *Way to Health* platform is able to collect metadata on participants' engagement with the platform to be able to track engagement with the interventions. For example, *Way to Health* can capture the type of, and date when, NRT modalities (gum, patch, lozenge) were ordered, dates that prescription medication reimbursements were requested, survey completion dates, information on the delivery of emails and text messages as well as capturing verbatim responses to all delivered text messages. By this means, the study will be able to capture adherence to the EFT mobile application and participants' interactions with EFT cues over a six-month period. Google Analytics of page views will potentially be used to supplement this engagement information, for patients who viewed resources but did not take action.

8.4. Data Security

An additional level of protection against research risks entails a series of data security elements that ensure the maintenance of confidentiality of all study data and participant information. The Data Coordinating Center will reside at Penn. The *Way to Health* system has a set of governing policies to ensure strict maintenance of all study data, including protected health information (PHI). These policies, in full. Can be accessed at: https://policy.waytohealth.org/#17-data-integrity-policy

In brief, all *Way to Health* servers are managed by Penn Digital Academic Research Transformation (DART), formerly Penn Medicine Academic Computer Services (PMACS). These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. All data at-rest is stored on encrypted disks using encryption keys managed by *Way to Health*. Encrypted disks use AES encryption with a minimum of 256-bit keys, or keys and ciphers of equivalent or higher cryptographic strength. User passwords are never stored in clear text; they are "salted" and "hashed" to eliminate data leakage. All data transmission is encrypted end to end using encryption keys managed by *Way to Health*. Transmission encryption keys use a minimum of 2048-bit RSA keys, or keys and ciphers

of equivalent or higher cryptographic strength (e.g., 256-bit AES session keys in the case of IPsec encryption).

Security is paramount. To monitor ongoing usage of the system and identify unauthorized usage of the system, all access to the application and the database are logged automatically. The *Way to Health* team perform regular (at least monthly) vulnerability scans of their systems to identify and patch any known vulnerabilities. They also run Intrusion Detection Systems (IDS) to identify unauthorized system access. *Way to Health* also has policies and procedures in place for system recovery following a disruption resulting from a disaster (such as extended outages). *Way to Health* has automated procedures to create and maintain retrievable data utilizing their Backup Service. These backup procedures are run on a daily basis and stored in a different location. Backups are encrypted. Backups are retained for a rolling 14 day period. Recovery from backups is also tested on a quarterly basis.

Data downloads are generally prohibited by *Way to Health* policy. Where appropriate, most datasets are blinded of all personally identifiable information when exported for analysis. A limited number of exports including identifiers exist to assist research staff with recruitment tracking and study management efforts. These datasets are only accessible to certain user roles. These user roles are required to sign and adhere to a *Way to Health* Security Agreement. The Way to Health data managers will formalize secure data protocols for transfer of *Way to Health* data to the PAIR Center's secure fire-walled server, with restricted access by PAIR Center's full-time data managers and appropriate analytic staff. No study data will be stored on stand-alone computers and laptops.

8.5. Risk-Benefit Ratio

The potential risks to human subjects attributable to participating in this trial are minimal. Risks include:

(1) Risk of breach of confidentiality of personal health information (PHI); however, there are strong data safeguards in place to prevent confidentiality breaches, as described in § 8.4. Data Security.

(2) Risk of a breach in privacy during collection of urine or blood samples for biochemical confirmation of abstinence. We are providing three options for patients to submit their samples, with patients paid in recognition of this additional research burden. Dependent on the health system, a lab sample may be submitted through their health system's labs, local Quest labs, with all participants able to request ExamOne, a mobile service that collects samples in patients' homes. All companies comply with Health Insurance Portability Accountability Act (HIPAA) regulations, have policies in place to ensure patient privacy, and are observing patient safety protocols during the COVID-19 pandemic (which will be communicated to participants).

(3) Risk of adverse effects of pharmacotherapies prescribed by a physician. These same risks arise in usual clinical practice in which these medications are routinely recommended for smokers. The research study is removing the cost barrier for patients to receive pharmacotherapies, but physicians must still prescribe pharmacotherapies based on their best clinical judgment of known benefits, risks and side effects. Thus, these risks do not qualify as incremental risks of the research itself. Under the Common Rule, Institutional Review Boards (IRBs) are charged with considering "only those risks and benefits that

may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)."

Smoking-related illness still remains the leading cause of preventable death in the United States. Enrolling large numbers of smokers in a study in which all will be offered some form of assistance with cessation provides high expected benefits, both to enrolled participants and in terms of the knowledge to be gained. In light of the tremendous benefits to public health and individuals of developing more effective programs, as well as our efforts, outlined above, to mitigate all risks associated with this study, we believe that this study presents a highly favorable risk-benefit ratio for participation.

9. Analysis

9.1. Sample Size and Statistical Power Calculations

Based on our previous trials, and considering the population to be studied in the present trial, we anticipate a six-month prolonged abstinence rate of 2.5% with basic usual care. Although somewhat higher rates of cessation were observed in usual care during the National Lung Screening Trial, that trial used self-report to determine smoking status and enrolled patients who were interested in improving their health, rather than the non-selected patients to be enrolled in this pragmatic trial. We wish to detect absolute differences of at least 5 percentage points in abstinence rates between any of the three intervention arms and basic usual care or between any two of the three intervention arms (six total contrasts). This difference is clinically important given the dramatic health benefits of stopping smoking and the low rates of success of available interventions, and is identical to that used to determine power in our recent pragmatic RCTs.

Contrast	Health systems contributing data to the analysis
AAR vs. AAR + pharmacotherapy	3 health systems, excluding Kaiser
AAR vs. AAR + pharmacotherapy + incentives	3 health systems, excluding Kaiser
AAR vs. AAR + pharmacotherapy + incentives + EFT	3 health systems, excluding Kaiser
AAR + pharmacotherapy vs. AAR + pharmacotherapy + incentives	All 4 health systems
AAR + pharmacotherapy vs. AAR + pharmacotherapy + incentives + EFT	All 4 health systems
AAR + pharmacotherapy + incentive vs. AAR + pharmacotherapy + incentives + EFT	All 4 health systems

As detailed in §6.2 Assignment, we project enrollment of 470 patients in the basic usual care arm, and 910 patients in each of intervention Arms 2-4. We used statistical simulations to understand the power under various settings with 1,000 iterations at each setting. All simulations were performed in R version 3.5.0.

Power for interaction analysis: Achieving the target sample size will provide >80% power to detect differences of at least 10 percentage points for statistical interactions between the comparative effects of two interventions and dichotomous patient characteristics (e.g., black vs. white) in which the less commonly observed characteristic is represented among at least 25% of participants. This calculation of

power to detect statistical interactions uses an alpha level of 0.10, as in our prior study of modifiers of the effects of smoking cessation interventions.

9.2. Statistical Analysis

9.2.1. Primary Analytic Approaches

We specify three sets of inferential analyses in our Statistical Analysis Plan (see accompanying documents. First, our primary analytic approach will be to conduct intention-to-treat (ITT) analyses using a generalized linear model (GLM) with a logit link function to estimate the effect of treatment arms to usual care. All models will be adjusted for health system, and patient level covariates. Intention-to-treat analyses will include all randomized patients regardless of their adherence to protocol or the actual treatment received. Patients will be analyzed using their assigned treatment arm. All events occurring within the specified time periods will be included in the analysis regardless of whether the patient adheres to the protocol. Information from patients who withdraw their consent to participate in the study will be included up to the time when they withdraw their consent. The primary analysis for all primary, and secondary endpoints will be performed as intent-to-treat analyses. We plan to do sensitivity analysis where we only include health system as fixed effects and no patient-level covariates. If we find any patient covariate that we pre-specified for inclusion in the model and has missing values > 15% then the above unadjusted analysis would become our primary analysis.

All analyses will be conducted with adjustment for the pre-specified, patient-level, baseline covariates. We plan to include fixed effect terms for health system, thereby both preventing confounding by system and appropriately adjusting variance estimates to account for potential similarities among patients within a given system.

9.2.2. Approach to Missing Data

We will follow all CONSORT reporting guidelines (www.equator-network.org). Statisticians blinded to trial arm will prepare reports describing all data using appropriate summary statistics with estimates of variance and graphical representations of the distributions. We will compare distributions of the characteristics of enrolled patients to those of all patients identified as potentially eligible to quantify the trial's external validity. Our first step in handling missingness will be to report all reasons for data missingness in detailed CONSORT diagrams, as we have done in prior RCTs. Incidence of missing data, particularly the primary endpoint, is expected to be low. Missingness in primary outcome can occur in following situations:

- No response to short survey
- Self-reported quit but no lab sample submitted in time

We will fully describe all data that are missing at each time point. Our secondary analyses will use multiple imputation methods that assume data are missing at random by including all baseline characteristics, treatment assignment, and reasons for missingness in the imputation model. This approach allows use of baseline and available follow-up data (e.g., at baseline and 6 months) to inform the generation of values for subsequent missing data points (e.g., at 12 months), and properly adjusts for the uncertainty in the resulting imputed values. We also plan to conduct sensitivity analyses using

pattern-mixtures models to explore and potentially adjust for patterns of missingness.

9.2.3. Heterogeneity of Treatment Effects

Heterogeneous treatment effects (HTE) will be explored by testing statistical interactions between pre-selected patient characteristics and each contrast between 4 interventions in logistic regression models. This will help guide future targeting of optimal interventions for individual patients. We will evaluate each interaction term separately in a model adjusted for all main effects and health system to estimate stratum-specific effects of each characteristic on the interventions' effectiveness. We plan to report results from a fully adjusted model that retains all significant interaction terms. We will limit our search for heterogeneity of treatment effects to variables selected based on *a priori* hypotheses. Our preliminary list of effect modifiers are: demographics (e.g., age, gender, race, ethnicity, rurality, income, socioeconomic status, insurance, etc.), lung cancer screening history, lung cancer screening results, tobacco dependence, temporal discounting, presence of mental health diagnoses, presence of chronic co-morbid illnesses, financial wellbeing, and internet access.

10. Oversight

10.1. Investigative Team

The study team is led by a noted expert in medical and research ethics whose prior experiences designing and conducting large randomized trials will augment the quality of research protections in this study. PI Scott Halpern has an appointment in Penn's Department of Medical Ethics and Health Policy, is one of ~200 fellows of the Hastings Center, the world's leading bioethics research institution. He has served as the Vice Chair of the American Thoracic Society Ethics & Conflict of Interest Committee, and has been a member of the Editorial Board of the American Journal of Bioethics since 2014. In 2008 he received the United States' most prestigious awards for young bioethicists, the Greenwall Foundation Faculty Scholar Award in Bioethics. He has consulted on ethical matters for the NIH, CDC, FDA, National Academy of Medicine (and its predecessor the Institute of Medicine), the United Network for Organ Sharing, The World Bank, and two Advisory Committees to the U.S. Secretary for Health and Human Services. Since receiving his Masters of Bioethics in 2002, Dr. Halpern has published widely on ethical issues in the design and conduct of clinical trials, the use of financial incentives for research participation, the ethical issues associated with the allocation of scarce resources, and a variety of other issues.

All study investigators and staff at Penn have completed the online training program, Collaborative Institutional Training Initiative (CITI), and will maintain active certifications throughout the study. Our collaborators at Geisinger, Henry Ford, and Kaiser will similarly be required to undertake CITI or equivalent trainings as part of the IRB Authorization Agreements (IAAs) that will be executed with the Penn IRB, which is acting as the central IRB of record for this trial. Penn team members are further required to maintain HIPAA certification and Good Clinical Practice certification. In aggregate, these materials provide systematic training in the fundamental issues underlying the responsible conduct of research.

10.2. Regulatory Approvals

The University of Pennsylvania IRB (IRB00009947) will serve as the central IRB of record for this trial. This single-IRB approach is now required for new grants for multicenter clinical trials to the National Institutes of Health, and we believe it is appropriate for this proposed trial as well. We will execute reliance agreements, or SMART IRB agreements, with the IRBs at Geisinger (IRB00008345), Henry Ford (IRB00000253), Kaiser (IRB00000403), and Lancaster General Hospital (IRB00000015). After IRB approvals, we will register the trial at ClinicalTrials.gov prior to enrollment of the first participant and submit clinical trial results to ClinicalTrials.gov within 12 months from the primary completion date.

At each of the four participating study sites, the study is staffed by a site PI, Co-I(s) and a research support team, namely a project manager and a data manager and/or programmer. The University of Pennsylvania Health System operates separate lung cancer screening programs within Philadelphia and Lancaster General Hospital (LGH). LGH is considered under the umbrella term 'Penn' as it is the same HIPAA entity; however, a standing reliance agreement additionally needs to be executed for purposes of this study.

The University of Pennsylvania has a dedicated full-time project manager who will coordinate with Site PIs and their project managers to ensure that all parties have the most current version of the study protocol and supplementary materials. The lead project manager at Penn will be the Penn IRB Point of Contact responsible for adding into Penn's Human Subjects Electronic Research Application (HS-ERA) system the relying study sites once the IRB Authorization Agreements have been executed. The Penn IRB Point of Contact will additionally be responsible for submitting protocol-wide modifications that impact all study sites, and where needed, any site-specific modifications. She will communicate all changes to the four site PIs and project managers at each health system during the process of submission to HS-ERA, and disseminate IRB approval letters after modification approvals. Our four site PIs and project managers will be responsible for reporting any deviations, exceptions, and reportable events from their health system within required timeframes to the IRB Point of Contact and PI Halpern, who will promptly notify the Penn IRB through HS-ERA. The Penn IRB will notify the local site IRB if it is found that those events qualify as an unanticipated problem involving risks to subjects or others. If this determination requires external reporting to the FDA or OHRP, the Penn IRB will work with the local site IRB to get their input before an external report is sent.

The collection and management of longitudinal outcomes data will occur primarily from patient self-report data submitted through the online *Way to Health* platform, managed by the University of Pennsylvania. As such, the Penn study team is able to generate aggregate patient accrual data for the multi-site enrollment tables required as part of the Continuing Review submission process. As part of data and safety monitoring plan, our DSMB recommendations will also be included in the Continuing Review submission, as will any reportable events or protocol deviations. Once a Continuing Review is approved by the Penn IRB, the IRB Point of Contact will distribute those IRB approvals to the other three health systems through our established channels.

A formal closure request will be submitted once study activity has been completed at a relying site once there is no further access to identifiable subject data for research purposes. Study personnel at the relying site will send a closure form to the IRB Point of Contact for submission through HS-ERA.

10.3. Data and Safety Monitoring Board

To guide the safe and ethical conduct of this study, we have assembled a Data and Safety Monitoring Board (DSMB) with requisite expertise in lung cancer screening, smoking cessation, biostatistics, and the administration of programs to reduce smoking. The DSMB will be chaired by Renda Wiener, MD, MS, an expert in lung cancer screening and smoking cessation at Boston University. Other DSMB members will be Christopher Slatore, MD, another expert in lung cancer screening and smoking cessation at Oregon Health Sciences University, Joelle Fathi, DNP, a nurse practitioner with expertise in leading smoking cessation programs for older smokers, and Scott Evans, PhD, Professor and Director of the Biostatistics Center at George Washington University School of Public Health, and Dr. Neil Dickert, MD PhD, Assistant Professor of Medicine at Emory University School of Medicine. Dr. Dickert is an internationally recognized authority on research ethics, with particular expertise in the ethics of payments for research participation and alternatives to traditional informed consent.

The DSMB is primarily responsible for safeguarding the interests of trial participants, assessing the safety of the intervention during and at the end of the trial, and for monitoring the overall conduct of the clinical trial to assess the overall-risk benefit ratio of the intervention. The DSMB will be responsible for deciding whether to continue or terminate the trial based on patient safety. The DSMB may also determine whether amendments to the protocol or changes in study conduct are required in order to protect human subjects. Members of the DSMB will not be involved in the conduct of the trial.

Once convened, the DSMB will perform several duties. First, they will meet in the year prior to the study's implementation to review and approve the DSMB Charter, statistical analysis plan, research protocol, and plans for ongoing data and safety monitoring. As part of this initial meeting they will also determine the schedule for interim analyses and regularity of DSMB meetings (at least annually). Second, they will assess patient safety data and evaluate participant risk versus benefit. Third, they will make recommendations to ensure that any identified issues are appropriately addressed. The DSMB will make recommendations about study progress, safety, or trial continuation based on detection of any early evidence of harm. We do not plan to stop the trial early for evidence of effectiveness of the intervention because doing so would markedly reduce our power to detect heterogeneity of treatment effects – that is, which types of interventions best promote smoking cessation for which types of patients. We will propose to stop the trial (or a trial arm) early in the unlikely event that evidence arose of adverse effects of other types of measurable harm. Dr. Halpern (PI) will be directly responsible for identifying and reporting all serious adverse events, protocol deviations/violations and unanticipated events to the Penn IRB and DSMB. DSMB reports will be uploaded into Penn's HS-ERA system and communicated with the site PI and project manager at each health system.

10.4. Stakeholder Advisory Committee

Given the target population for this study, we anticipate a high number of economically and

educationally disadvantaged persons. We have assembled a Stakeholder Advisory Committee, which includes patient advisors who meet study eligibility criteria, to review study design and materials before trial launch. The Stakeholder Advisory Committee was established during the grant proposal process and includes research partners that represent the broad impact of smoking among underserved patients: community and policy organizations, clinician and payer leaders, and patients. These stakeholders are focused on empowering underserved low-income, low-education, black, and/or Hispanic communities; promoting and implementing public health programs; and/or preventing tobacco-associated disease. Michael Scott of the Center for Black Health & Equity (formerly the National African American Tobacco Prevention Network) serves as Lead Stakeholder Partner.

The SAC will operate throughout all years of the study to engage with the research team on study design, implementation, patient follow-up, analysis, and dissemination of study results. A SAC Charter was developed to help guide SAC roles and responsibilities, reimbursement, communication and meeting schedules, and committee expectations. The research team and SAC members will work as partners and uphold the principles of engagement that include: reciprocal relationships, partnerships, co-learning, and transparency, honesty, and trust. As such, partners will collaboratively identify agenda items for discussion, present key updates, and receive feedback throughout the course of the study. Broadly, SAC members will be asked to share opinions and strategies about how to best engage the patient population in the interventions throughout the course of the study; identify appropriate, patient-friendly ways to enroll patients in the study; advise the research team on how to scale up and implement smoking cessation strategies on the health system level; guide the research team in how to make sense of and share the study results; develop new and creative ways to help others learn from our successes and challenges as research partners; and evaluate the research team's engagement plan to ensure that it aligns with the Committee's goals and expertise.

The SAC will meet twice a year, supplemented by newsletters, phone calls as needed, and ad hoc meetings and workgroup email exchanges as stakeholders' availability and interests align. The goals of meetings will be: 1) co-learning through educational sessions on successful research engagement and patient-centric research practices, including those led by SAC members, 2) reviewing progress, including collaborative problem-solving for encountered or anticipated barriers, 3) establishing goals and delegating tasks for the subsequent year, and 4) forming closer relationships between the entire research team. All travel expenses will be covered for in-person meetings, as will any hardware or software computer needs to facilitate participation and regular contact with research team members collaborating on work products.

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Comparing Smoking Cessation Interventions among Underserved Patients Referred for Lung Cancer Screening: A Randomized Clinical Trial

Principal Investigator	Scott D. Halpern, MD, PhD
Funding Agency:	Patient-Centered Outcomes Research Institute
IRB Protocol Number	Pending
Clinical Trials.gov Number	Pending
Version Date:	May 1, 2019

Protocol Summary

Title	Comparing Smoking Cessation Interventions among Underserved Patients Referred for Lung Cancer Screening
Short Title	TBD
Principal Investigator	Scott D. Halpern, MD, PhD
Co-Investigators	*University of Pennsylvania:* Anil Vachani, MD, MS; Kevin Volpp, MD, PhD; Joanna Hart, MD, MS; Dylan Small, PhD; Alisa Stephens, ScD; *Kaiser Permanente Southern California:* Michael Gould, MD, MS; Mohamed Ismail, MD MPH; *Geisinger Health System:* Matthew Facktor, MD; Charlotte Collins, PhD; *Henry Ford Health System*: Christine Neslund-Dudas, PhD; Michael Simoff, MD; *SUNY Buffalo:* Leonard Epstein, PhD
Design	Pragmatic randomized clinical trial
Objectives	To compare the effectiveness of four interventions to promote sustained, biochemically confirmed smoking abstinence for 6 months among underserved smokers referred for lung cancer screening at four large U.S. health systems.
Trial Duration	4 years
Study Sites	The University of Pennsylvania Health System; Henry Ford Health System; Geisinger Health System; Kaiser Permanente Southern California
Sample Size	3,200 patients
Patient Eligibility	1) Age ≥ 18 years 2) Current smoker (≥ 5 cigarettes per day, not including e-cigarettes) 3) Has a low-dose computed tomography (LDCT) scan ordered by his or her physician 4) Underserved, defined as one or more of the following: i. Black ii. Hispanic iii. Rural residence iv. Low socioeconomic status, defined as one or both of: a. ≤ high-school education or less b. household income < 200% of the federal poverty line 5) Access to a phone with text messaging or the internet
Interventions	Patients will be individually randomized into 4 arms: 1. Basic usual care: Ask-Advise-Refer (AAR) approach 2. Enhanced usual care: usual care plus free nicotine replacement therapy and FDA-approved pharmacotherapies 3. Enhanced usual care plus a mobile health application that motivates patients

	to think about their future health by promoting episodic future thinking (EFT) 4. Enhanced usual care plus the mobile health application plus financial incentives to stop smoking
Outcomes	**Primary Outcome:** Biochemically confirmed smoking abstinence that is sustained for 6 months. **Secondary Outcomes:** Secondary smoking-related outcomes include point-prevalent quit rates at 1 and 3 months, and relapse rates at 12 and 18 months. Secondary patient-reported outcomes include: • Nicotine dependence • Motivation to quit • Self-efficacy related to cessation efforts • Perceived barriers to cessation • Anxiety • Health-related quality of life
Analysis of Primary Outcome	• Intention-to-treat approach, such that all patients meeting eligibility criteria who are randomized will be evaluated as assigned
Study Oversight	• A Stakeholder Advisory Committee comprising patients, representatives from community and policy organizations, and clinician and payer leaders will advise the investigators about study implementation, including through the review of patient-facing materials and by helping to mitigate any unforeseen risks or burdens that may arise • Trial oversight will be conducted by the University of Pennsylvania (Penn) Institutional Review Board (IRB00009947) as the central IRB of record, with reliance agreements executed with participating health systems' IRBs. • A Data and Safety Monitoring Board (DSMB) will be convened to review the trial protocol, address any safety concerns that may arise, and make recommendations regarding trial continuation, modification, or termination.

Contents

1. Abstract

Low-dose computed tomography (LDCT) screening reduces mortality among current and former smokers at high risk for lung cancer, and is widely recommended by national guidelines. LDCT also increases access to care and thus provides an opportunity to deliver smoking cessation interventions to current smokers in conjunction with this screening. As the burdens of smoking are greatest, and the effectiveness of standard interventions lowest, among patients who are black, Hispanic, from rural residences, and/or are less educated or have lower incomes, such underserved patients are at high risk for poor smoking-associated health outcomes. Correspondingly, they may stand to benefit preferentially from smoking cessation interventions delivered in conjunction with LDCT. However, it is unknown which interventions best promote cessation in the screening context. By comparing standard with incrementally more intensive interventions, this trial among 3,200 current smokers in four health systems will address the uncertainty health systems face regarding how best to help high-risk smokers quit.

2. Background and Rationale

Stopping smoking greatly reduces morbidity and mortality among patients eligible for lung cancer screening**.** Cigarettes remain the leading cause of preventable morbidity and mortality worldwide,[1,2] causing at least 5 million deaths annually, including half a million in the U.S.[2-4] The National Lung Screening Trial found that annually screening current and former heavy (at least 30 pack-years) smokers aged 55-75 using low-dose computed tomography (LDCT) reduces mortality.[5] Thus, annual LDCT screening is widely recommended by national guidelines.[6,7,8] Because more than 5 million Americans who are eligible for LDCT are current smokers,[9-10] and in light of evidence that smokers who quit while undergoing screening gain an average of 4 years of life expectancy due to reductions in lung cancer and other tobacco-related illnesses,[11-13] national guidelines recommend,[6, 14, 15] and the Centers for Medicare and Medicaid Services (CMS) requires,[16-17] that smoking cessation interventions be delivered as core components of LDCT screening programs. To successfully reduce harm from tobacco and promote cessation goals, we aim to expand the armamentarium of evidence-based strategies for smoking cessation. We propose conducting a 4-arm pragmatic randomized clinical trial among current smokers who are referred for lung cancer screening.

While there is limited evidence regarding the comparative effectiveness of different ways to promote smoking cessation, few studies have examined cessation strategies among underserved populations. Research suggests that **e**mbedding smoking cessation interventions within LDCT screening programs may be particularly beneficial for underserved patients because screening produces an extra clinical contact,[18-19] and because the burdens of smoking-related illnesses are greatest among patients who are black, Hispanic, and/or have low socioeconomic status (SES).[20-23] Enrollment in this study has been targeted towards racial minorities, ethnic minorities, low-income groups, and residents of rural areas to identify unique needs of this patient population in order to help them find their best support related to smoking cessation.

The approach currently used by most U.S. lung cancer screening sites is "Ask-Advise-Refer," whereby patients are asked if they smoke, advised of the benefits of cessation, and referred to local cessation resources including behavioral counseling.[24, 25] However, the overwhelming majority of patients exposed to this approach continue smoking.[26] The other commonly used approach is to provide free nicotine replacement therapy (NRT) and the two FDA-approved medicines for smoking cessation (varenicline and bupropion). Despite the wide adoption of pharmacotherapy interventions among health care systems in the US, this strategy also lacks evidence of effectiveness as part of LDCT screening. In a recent pragmatic trial in workplace settings, PI Halpern found that providing free access to cessation aids failed to promote cessation.[27] In contrast, financial incentives have been shown to be effective in improving health in a variety of areas, including smoking cessation. In the two largest smoking cessation trials, financial incentives totaling $600-800 were found to triple sustained smoking cessation rates compared with usual care groups 6 months after quitting.[27-28] Following a period of 6 months where incentives were discontinued, these differences between groups remained intact, supporting the use of incentives for sustainable cessation efforts.

Given the limited evidence regarding how best to promote smoking cessation in the context of LDCT screening programs, both the NIH[29] and National Academy of Medicine[15] have highlighted the need to identify more effective smoking cessation programs. Smokers tend to be "present-biased" with a propensity to discount future benefits (e.g., greater health following smoking cessation) in favor of immediate satisfactions (e.g. the pleasures of smoking). By contrast, cancer screening is an event that naturally motivates people to adopt a future orientation,[30] or state of prospection,[31] as they contemplate how their future lives may differ based on whether they receive reassuring or concerning results. This may explain why patients undergoing screening express increased motivation to quit smoking.[18,32] Thus, screening programs represent a prime setting within which to deploy a mobile health application, "Episodic Future Thinking" (EFT), that helps people imagine futures selves that are healthier and/or wealthier by virtue of having quit (and thus, having saved the money they would have spent on cigarettes). This study will also assess whether financial incentives may work in a complementary fashion to EFT – with incentives providing an immediate, extrinsic motivation to quit, and EFT helping to sustain abstinence by enhancing people's intrinsic motivations to be healthier and wealthier in the long term.

3. Objectives

3.1. Specific Aims

Our primary objective is to help underserved patients who are referred for lung cancer screening to quit smoking. We will complete three specific aims:

1. Compare the effectiveness of the two main interventions currently used to promote smoking cessation in the context of lung cancer screening:
    (i) Ask-Advise-Refer, and
    (ii) Ask-Advise-Refer plus free access to nicotine replacement therapy and FDA-approved pharmacologic cessation aids
2. Compare these standard approaches with multicomponent interventions that add one or both of:

(iii) A mobile health application that motivates patients to think about their future health through episodic future thinking, and
(iv) A mobile health application plus financial incentives for successfully quitting.

3. Assess heterogeneity in the effectiveness of these four interventions in promoting cessation among smokers that differ by race, ethnicity, income, education, rurality, tobacco dependence, and objectively reported and patient-perceived lung cancer screening results.

3.2. Primary Outcome

The primary outcome measure is sustained abstinence for 6 months, and will require self-report of smoking cessation followed by biochemical confirmation at 1, 3, and 6 months.

3.3. Secondary Outcomes

Secondary smoking-related outcomes include:

- Point-prevalent quit rates at 1 and 3 months, and relapse rates at 12 and 18 months

Secondary patient-reported outcomes (PROs), include:

- Nicotine dependence
- Motivation to quit
- Self-efficacy related to cessation efforts
- Urge to smoke
- Perceived barriers to cessation
- Anxiety
- Health-related quality of life

See §7.6. Baseline Survey and §7.9.2. Biochemical Testing for additional information on methods and study instruments used to measure outcomes for the trial.

4. Study Design

4.1. Overview

We will conduct a 4-arm randomized trial comparing these 4 interventions to promote sustained, biochemically confirmed smoking abstinence for 6 months among smokers in underserved demographic groups. The 3,200 participants to be enrolled will be current smokers who are black, Hispanic, and/or have low socioeconomic status (defined as household income <200% of the federal poverty line or a high school education or less) or rural residence who are referred for LDCT screening at 4 large health systems. Patients with LDCT orders will be identified via the electronic health record and further screened for eligibility. Eligible patients will enroll and completed the study using the NIH-funded *Way to Health* (WTH) portal. Consistent with pragmatic trials' goals to assess the real-world effectiveness of interventions among the full range of potential beneficiaries of the interventions, potential participants will be enrolled by default and allowed to opt-out from study participation.

The primary outcome will be biochemically confirmed, sustained abstinence from smoking tobacco for 6

months following participants' selected quit dates. We will conduct intention-to-treat analyses using logistic regression to compare the overall effectiveness of the interventions among all randomized participants. Because not all participants will engage with their assigned intervention in this pragmatic design with opt-out consent, we will also conduct secondary analyses to compare the specific efficacy of interventions, conditional on acceptance, using complier average treatment effect analyses. We will also compare effectiveness among p≥

atients who differ in terms of race, ethnicity, income, rurality, degree of tobacco dependence, and the results of their LDCT screens (concerning vs. reassuring results), testing for statistical interaction between these factors and treatment assignment to guide future targeting of optimal interventions for individual patients.

4.2. Study Setting

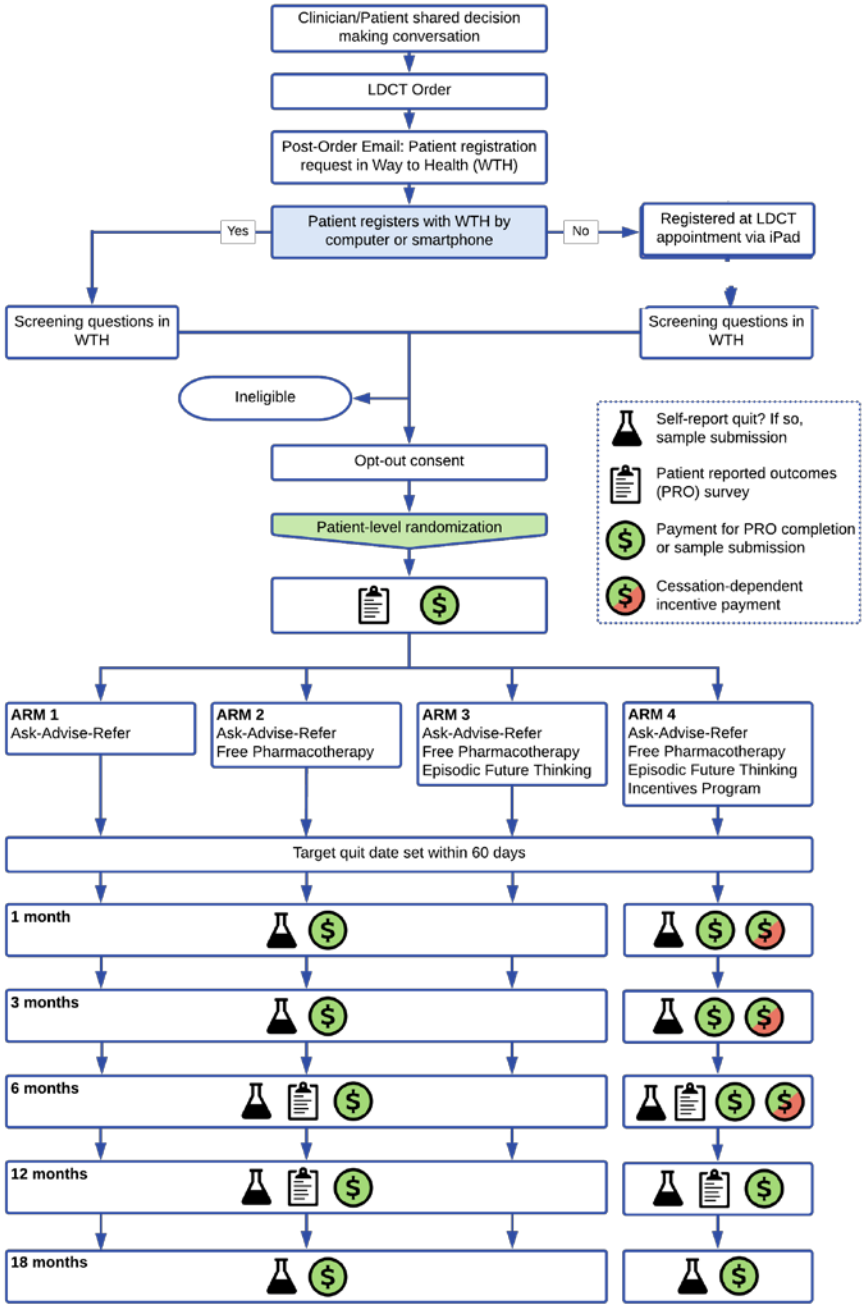
We will test the interventions during the course of providing usual care among underserved patients who have been referred for lung cancer screening in the outpatient setting within four health systems: University of Pennsylvania Health System (Penn), Geisinger Health System (Geisinger), Kaiser Permanente Southern California (Kaiser), and Henry Ford Health System (Henry Ford). These health systems were purposefully chosen as each serves a core constituent of our underserved patient groups. Kaiser is an integrated health system in Southern California that serves many Hispanic patients, as well as those who are black and low-SES. Geisinger serves patients who are predominantly from rural residences in Pennsylvania, and roughly half are low-SES. Henry Ford serves patients in the Detroit Metro area, where approximately 35% of patients are black and/or of low SES. Serving the Philadelphia Metro area, nearly half of the Penn's patients are black, and many are low-SES.

Reflecting the real-world nature of this pragmatic trial, all recruitment outreach efforts will be conducted by non-study health system personnel who facilitate LDCT screening visits in radiology outpatient settings or dedicated lung cancer screening clinics. Additional outreach will be through the health systems' patient portals, with all health systems using a common electronic health record platform, EPIC. There are no on-the-ground research staff within the outpatient settings for this pragmatic clinical trial.

4.3. Schema

This is a prospective randomized controlled trial with longitudinal follow-up of patients over 18 months.

Figure 1. Study Schema



5. Subject Recruitment

5.1. Accrual and Duration

Accrual will proceed over 32 months, beginning at the University of Pennsylvania in March 2020 and followed by the other three health systems in May 2020. We expect to accrue 3,200 patients over a 32-month period; however, the clinical trial will proceed over 4 years, to account for the longitudinal follow-up of enrolled patients of up to 18 months.

Although all enrolled patients will be contacted for a minimum of 12 months to complete 12-month surveys, only patients who show continued self-reported abstinence will be contacted for the full 18 months to track relapse.

5.2. Inclusion Criteria

All of the following patient inclusion criteria must be met:

1) Age ≥ 18 years
2) Current smoker (≥ 5 cigarettes per day, not including e-cigarettes)
3) Has a low-dose computed tomography (LDCT) scan ordered by his or her physician
4) Underserved, defined as one or more of the following:
    v. Black
    vi. Hispanic
    vii. Rural residence
    viii. Low socioeconomic status, defined as one or both of:
        a. ≤ high-school education or less
        b. household income < 200% of the federal poverty line
5) Access to a phone with text messaging or the internet

It is expected that LDCT orders will be placed by physicians in line with national screening guidelines, i.e., patients with a ≥ 30 pack-year smoking history and tobacco use within the past 15 years. The majority of enrolled patients are expected to be ≥ 55 years; however, patients < 55 years meeting all other eligibility criteria are eligible for this clinical trial.

5.3. Participant Remuneration

The 18-month maximal payment schedule for surveys, sample collections, and financial incentives is given below. All enrolled participants will be asked to complete 6-month and 12-month surveys, regardless of their self-reported abstinence status. Participants are only required to submit biochemical samples if they first self-report abstinence at the 1-, 3-, 6-, 12-, and 18-month time points (see §7.9. Longitudinal Assessments). If patients are assigned to Arm 4, they will additionally be eligible to receive up to $600 in financial incentives contingent on their continued biologically-confirmed abstinence at 1-, 3-, and 6-month time points. Participants in Arm 4 are therefore eligible to receive a maximal payment amount for surveys, sample collection, and incentives of $1,100.

Time Period	*Maximum Remuneration Amount*		
	Surveys	*Biochemical Samples*	*Incentives (Arm 4 only)*
Baseline	$50		
1 month		$50	$100
3 months		$50	$200
6 months	$50	$50	$300
12 months	$50	$100	
18 months		$100	
Total Remuneration	$150	$350	$600

Patients will receive payments through issuance of GreenPhire ClinCards that will be mailed to participants within 10 days of enrollment. These ClinCards can be used in the same manner as a credit card. ClinCards can be re-loaded remotely with additional funds by study team members via the *Way to Health* platform after completion of study activities.

6. Randomization

6.1. Groups

We plan to compare the effectiveness of four interventions, as follows:

Arm 1: Usual care

Participants randomized to this basic usual care arm will receive the usual care approach, Ask-Advise-Refer, which is a standard approach in which clinicians ask smokers about their desire to quit smoking, advise them to quit, and refer them to resources such as hotlines or smoking cessation classes.

Arm 2: Enhanced usual care

Participants randomized to this arm will receive the usual care of Ask-Advise-Refer as well as access to pharmacotherapy (varenicline/Chantix or bupropion/Zyban) and nicotine replacement therapy (NRT).

Arm 3: Enhanced usual care plus a mobile health application

Participants in this arm will receive all aspects of enhanced usual care plus an intervention to promote episodic future thinking (EFT). EFT has been shown to reliably reduce discounting of the future. Patients will practice using EFT cues to envision the "future is now" between the time of enrollment and the quit date, and will then receive cues from the quit date through the end of the intervention period, 6 months later, unless they ask to stop receiving cues sooner.

Arm 4: Enhanced usual care plus the mobile health application and financial incentives

Participants in this arm will receive all aspects of Arm 3 plus an incentive plan in which they will be informed of their eligibility to earn $100, $200, and $300 if they submit negative tests for nicotine metabolites at 1, 3, and 6 months following the quit date, respectively.

6.2. Assignment

Participants will be randomized individually, stratified by health system, to 1 of the 4 arms using random number generation within the *Way to Health* platform. At Penn, Geisinger, and Henry Ford sites, 25% of enrolled participants will be assigned to each of the 4 arms. Because Kaiser already offers free cessation aids to all its patients, there exists no basic usual care arm; thus, patients enrolled at Kaiser sites will only be assigned to Arms 2-4, each with a 33% probability. Based on the expected accrual at each of the four health systems we expect that overall there will be 470 patients in basic usual care (Arm 1) and 910 patients in each of intervention Arms 2-4.

7. Study Procedures

7.1. Eligibility Screening

An EHR-based algorithm will identify potentially eligible patients who have had a LDCT scan ordered by their physicians. At all health systems, placement of a LDCT order signifies that a patient has a ≥ 30 pack-year smoking history and tobacco use within the past 15 years. The presence of a LDCT order among adult patients will be the only criterion used by the EHR algorithm to flag further approach to complete secondary eligibility questions related to demographics (i.e., to assess their underserved status) and smoking status (i.e., to assess if a current smoker) , as described in §7.2.

Although some demographic attributes (e.g., race, ethnicity) can be assessed somewhat reliably solely on the basis of EHR-based data, rurality is under-captured by zip code alone, and socio-economic status (SES) cannot be reliably assessed without patient self-report of their education level and household income. Given that participants can qualify for the study on the basis of race, ethnicity, rurality, **or** SES, the EHR-based algorithm would be unable to make a definitive determination of true underserved status if only some of these demographic attributes were incorporated from the EHR into the algorithm.

We have chosen not to incorporate EHR-derived data on current smoking status into the algorithm for scientific and logistical reasons. First, because our target population is those who smoke ≥5 cigarettes per day (excluding e-cigarettes), self-report is a more accurate means of assessing eligibility than EHR-derived data. Second, there are considerable logistical advantages to approaching all adult patients presenting for LDCT screenings. Specifically, these approach does not require health system staff to differentiate between eligible and ineligible patients in order to proceed with enrollment, but rather can embed the screening into the routine operational workflow for non-study health system personnel at the LDCT screening sites. We will permit patients ≥ 18 years with a LDCT order to participate in the trial given that some integrated health systems like Kaiser allow LDCT orders to be placed for patients < 55 years (and reimburse accordingly). We anticipate that approaching all adult patients during lung cancer screening will result in recruitment of some patients in the 50-55 age range, but believe that this will connect more underserved patients who are at risk for lung cancer with interventions that could help them quit smoking.

7.2. Recruitment

There are two complementary pathways to direct patients to the *Way to Health* platform to answer further eligibility questions. First, as soon as the LDCT order is placed, the EHR algorithm will send email messages through the patient portal to potentially eligible patients who have valid email addresses listed within the EHR. The EHR system also has the capacity to alert the study teams at each health system when this event occurs. Email invitations will direct patients to the *Way to Health* platform prior to their lung cancer screening visit. Email invitations will only be sent through this approach at two of the four health systems (Penn and Geisinger). At the remaining two health systems (Kaiser and Henry Ford) the first point of contact will be at their lung cancer screening visit at either a dedicated lung cancer screening clinic or an outpatient radiology site. Non-study, health system registration personnel at the front desk will receive an EHR-based flag that reminds them to give an iPad tablet to all adult

patients referred for a LDCT scan as part of their admissions process. For ease of embedding in the clinic workflow, the iPad will be given to all adult patients and not just smokers.

7.3. *Way to Health* Registration

Way to Health is a comprehensive online research platform developed by the University of Pennsylvania that will be deployed for this study. *Way to Health* links a web-based participant portal to a variety of peripheral devices (including cell phones) for assessing health behaviors; provides an infrastructure for communicating with and providing feedback to patients by email or text message at patients' discretion; mediates electronic transfer of payments for study tasks or incentives for smoking cessation; delivers mobile health applications, such as EFT; and administers surveys.

The *Way to Health* platform for this study will be accessible in both English and Spanish. The email invitation and iPads will have easy-to-follow instructions for registering in *Way to Health* and patients will also be given information about a hotline to call for English or Spanish assistance with navigating through the website. After registration in *Way to Health*, patients will be asked whether they are a current smoker (smoke $\geq$ 5 cigarettes per day; not including e-cigarettes), and additional eligibility criteria related to race, ethnicity, income, education, rural residency, and phone or internet access. Patients who are not eligible because they do not have a phone or internet access, or do not fall into one of the underserved categories, will be provided with information about local resources to help them quit smoking.

We will build an EPIC automation to identify patients who have presented for their LDCT screening appointment, but did not register in *Way to Health* or complete the enrollment process. This situation could happen in instances where the participants were called back to the CT scanner before being given an iPad, or they were given an iPad but had insufficient time to finish registration and enrollment prior to being called back. Staff within each health system will email and/or phone patients within 10 days of the LDCT screening visit to provide them with an additional opportunity and encouragement to enroll.

7.4. Waivers of Consent and HIPAA Authorization

7.4.1. Waiver of Informed Consent

We will seek approval from the University of Pennsylvania (Penn) IRB, as the central IRB of record, to conduct the trial using an opt-out consent process. This approach is known as a *waiver or alteration of the requirement for individual informed consent* and is advocated for pragmatic trials testing methods for comparing and improving the delivery of established interventions within health care systems.[33-36] Recent NIH-funded research by our group and others reveals that patients generally endorse opt-out consent or simple notification approaches in pragmatic trials when such mechanisms help achieve the goals of the study.[37-39] Although large-scale, pragmatic, comparative effectiveness trials have previously been undertaken without consent at all, including by PI Halpern,[40] both our investigative team and our study's Stakeholder Advisory Committee strongly advocated for an opt-out consent process for this underserved population. Directly following eligibility screening, eligible participants will receive messaging in *Way to Health* about this voluntary program, will be directed to further information, and

given the opportunity to easily opt-out.

Below we describe the many reasons why an opt-out enrollment is appropriate for this trial.

1) The study presents no more than minimal risk to research participants. This is because the risks attributable to trial participation relate only to matters of data confidentiality.
2) An opt-out design is essential to answer the questions we are interested in: how might smoking abstinence be sustained if the health systems actually rolled out the interventions to be tested among its patients, and how do these interventions compare in terms of their effectiveness? In designing this pragmatic trial, we aimed to mimic a real-world setting with limited resources; opt-out consent, whereby patients are engaged with the program unless they actively choose otherwise, is how such programs would be rolled out in the real world. As programs similar to the current trial are being developed and disseminated across the country, it is imperative that we examine how interventions perform across diverse health systems with unique patient populations
3) Due to the large sample size needed for this study it would be impractical to employ study staff to manually recruit and consent 3,200 participants across multiple health systems. Traditional recruitment, outreach, and consent by study staff for this trial would exhaust all of our financial and labor resources, as well as significantly lengthen the time needed to conduct this trial. It would be impractical to conduct this study in the traditional manner and improbable that we would be able to complete such a trial with the resources we have available. Using an opt-out approach will allow this research to be conducted in a more time-efficient manner and will allow for more of the study resources to be used on the participants who are being treated rather than on materials that are aimed at recruitment.
4) Related to the above reason for using an opt-out design, standard procedure for research is to recruit, enroll and treat participants via an opt-in approach. This approach, while valid, only reaches about 15% of the target population who actually opt-in to the program, reducing the generalizability of the obtained results. The remaining 85% of at risk potential participants go untreated and researchers are left unsure if the interventions that were effective in the population that self-selected into the study will be effective with those who were not treated. Conducting this research using an opt-out enrollment will help us better understand how effective these interventions will be with the total population of interest, rather than with just highly motivated individuals.
5) Employing a waiver of consent for this trial will help to connect high-risk smokers to potentially helpful treatments that they may not otherwise seek out. Enrolling large numbers of smokers in a study in which all will be offered some form of assistance with cessation provides high expected benefits, both to enrolled participants and in terms of the knowledge to be gained. While smoking rates have reduced to 18% in the United States, smoking related illness still remains the leading cause of preventable death in the United States. More than 75% of current American smokers wish to quit; 45% do quit for at least a day each year; and anti-smoking policies, new pharmaceuticals, and behavioral modification programs offer promise to help them. Nevertheless, only 2-3% of smokers attain prolonged abstinence annually.

Given this high interest in quitting smoking, and low rates of successfully sustaining quit attempts with currently available programs, opt-out consent will ensure that all smokers will have the same access to

potentially helpful programs without the added barrier of completing a lengthy enrollment/consent process. Findings of the study will be published, and if successful, this trial could serve as a model for health systems across the country to implement similar programs.

7.4.2. Waiver of HIPAA Authorization

This trial will be conducted with a waiver of HIPAA authorization in accordance with the provisions for using protected health information (PHI) set forth in 45 CFR 46, § 164.512 (i) as follows:

1. The researchers require access to protected health information (PHI) in order to conduct the research.
2. The research cannot be practicably conducted without the waiver.
3. The use or disclosure of PHI poses no more than minimal risk to participants.

The research could not be practically done without access to PHI as multiple datasets and data from multiple time points need to be linked in order to evaluate secondary outcomes to answer our study questions. The study is using the minimum necessary elements of PHI to achieve these goals-- 1) patient identifiers are necessary to enable linkages to the EHR, and 2) patients' contact information is necessary to enable longitudinal assessments. See §8.2. Data Management.

7.5. Allocation

Participants will be randomized in the *Way to Health* platform to one of the four study arms, as described in §6.2., at which point patients are considered assigned to the Intention-to-Treat analyses.

7.6. Baseline Survey

Participants are asked to complete a ~20-minute baseline survey assessing the following:

- Nicotine dependence. *The Fagerström Test for Nicotine Dependence (FTND) is a widely used and validated 6-item measure to assess the intensity of physical addiction.*
- Motivation to quit. *The Stages of Change (SOC) is a validated 1-item measure to assess patient's self-reported motivation to quit.*
- Self-efficacy related to cessation efforts. *We will use the 10-item situational measure of self-efficacy to measure patients' self-efficacy to quit smoking.*
- Urge to smoke. *The Questionnaire on Smoking Urges-Brief (QSU-Brief) is a validated 10-item scale used to measure patients' urge to smoke.*
- Perceived barriers to cessation. *The Challenges to Stopping Smoking Scale (CSS-21) is a validated 21-item measure to assess patients' perceived barriers to smoking cessation. The CSS-21 has two sub-scales: intrinsic factors (physical, psychological or cognitive aspects of quitting) and extrinsic factors (social or environmental aspects of quitting).*
- Anxiety. *The Hospital Anxiety and Depression Scale (HADS) is a widely used 14-item tool to assess psychological distress in non-psychiatric patients and consists of two subscales, Anxiety and Depression.*
- Health-related quality of life. *The EuroQuol Group's EQ-5D scale is a 25-item validated scale used to assess patients' perceived health-related quality of life across the domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.*

- Household members. *Participants will be asked about their marital status and whether anyone in their household has a history of lung cancer or currently smokes.*
- Smoking history. *Number of prior quit attempts and number of years smoking.*
- Temporal (or "delay") discounting. *We will use a 5-item, adjusting-delay task developed by Co-I Epstein and colleagues.*

7.7. Setting a Quit Date

Participants are asked to set a quit date within the next 60 days. Each patient's selected quit date will be their "day 0" – the point from which all subsequent study dates and endpoints will be measured. Participants will receive email and/or text-message reminders at 14, 7, and 1 day prior to their selected quit date. A short assessment aimed at determining smoking status will be given at 1 month and those who report having successfully quit will be asked to undergo a urine cotinine and anabasine test (see sections §7.9.1. and §7.9.2.). Patients who self-report that they are still smoking at 1 month will return to "day 0" and have one additional chance to document abstinence 1 month later. In total, patients have a maximum of 90 days from enrollment to quit smoking.

7.8. Intervention Assignment

Participants are directed on the *Way to Health* platform to information specific to their randomization arm. Between enrollment and the quit date, patients may obtain free cessation aids (arms 2-4), develop and practice cues for use in the EFT intervention (arms 3 and 4), or receive financial incentives (arm 4), as detailed below.

7.8.1. Ask-Advise-Refer

On the *Way to Health* platform, participants will be able to view standard information such as the national quit hotline and local health system resources (e.g., Penn's smoking cessation clinic) and will be informed that they will be sent emails and/or texts at 1, 3 and 6 months to assess cessation status. Patients will be advised to speak with their own clinician about any other available local resources. We conceive that information on *Way to Health* will act to reinforce any Ask-Advise-Refer information already given to participants when their physicians placed the LDCT order.

7.8.2. Cessation Aids

Monthly supplies of NRT products can be ordered directly, free of charge, through the *Way to Health* web-based interface, and distributed via mail by beBetter Health. Participants can choose to select either patches, gums, or lozenges. NRT product information, recommended dosage based on their current smoking patterns, and side effects will be available of the website, with a link to the product website. Once selected, all shipping charges will be paid by the study. Similar information will be provided for two FDA-approved pharmacotherapies, varenicline and bupropion, with information alerting interested participants to seek a prescription from their clinician. Participants who choose to pursue a pharmacotherapy prescription from their physicians will be able to download a voucher from *Way to Health* to fill the prescription at select CVS stores in their area at no cost to them. CVS will invoice The University of Pennsylvania directly for the pharmacotherapy co-payments under an executed agreement.

7.8.3. Episodic Future Thinking

Participants will have the option of watching several short bilingual videos on the *Way to Health* platform that will help guide them through the process of developing personalized "EFT cues" that can be accessed over the next six months. Videos will describe EFT and how it's thought to work, specifics on how to generate good EFT cues, and address commonly cited barriers to accessing and using cues. Between the time of enrollment and the quit date, participants will practice generating their own EFT cues to envision the "future is now", by writing out positive, vivid descriptions of events that they're looking forward to in the future. All participants are instructed to imagine and describe in detail events that are positive, specific, and vivid. Participants are prompted to describe specific details of their events, including who was there, what was happening, where the event took place, and how they felt. Participants are instructed to describe the events as though they were currently happening.
Over the intervention period, *Way to Health* will then regularly prompt participants by text with their pre-specified EFT cues to envision a future, healthier self that has achieved his or her goal of quitting smoking. Participants will receive cues on a pre-determined schedule as well as on-demand from the quit date through the end of the intervention period, six months later, unless they ask to stop receiving cues sooner.

7.8.4. Financial Incentives

Participants will be informed of an incentive plan for successfully quitting and maintaining abstinence over six months. Participants will be informed of their eligibility to earn $100, $200, and $300 if they submit negative tests for nicotine metabolites at 1, 3, and 6 months following their target quit date, respectively. Participants will be informed of the need for biochemical testing to be eligible to receive payments (see §7.9.2). Participants will receive payments through deposition of additional funds directly onto their GreenPhire ClinCard, which they received in the mail after completion of the initial baseline survey.

7.9. Longitudinal Assessments

This is a longitudinal study whereby participants will repeatedly be asked to complete (i) smoking status updates, (ii) sample submissions, and (iii) patient-reported outcomes (PRO) surveys. During the enrollment process, participants will be indicate on their profile whether they prefer to be contacted by the study team by text message, email, or both modalities. Participants will then receive a notification via text message or email when they are required to complete one of these activities at a given time point. Each text message or email will include a link to the *Way to Health* website as well as information about what activity they need to complete. When a participants logs onto the website, a notification on the homepage will prompt him or her to complete the appropriate survey or link them to instructions on how to complete a sample submission.

7.9.1. Smoking Status Updates

Short assessments aimed at determining smoking status will be emailed and/or texted to participants at 1 month, 3 months, 6 months, 12 months, and 18 months. Assessments will take < 2 minutes to complete and will assess the use of cigarettes, NRT, and e-cigarettes. Assessments can be completed using their preferred modalities: via phone (by texting Y or N responses to questions) or via a link to the

Way to Health platform. Those who achieve abstinence at a given time point will continue to be queried regarding their abstinence at the next time point, and invited to submit samples if they continue to self-report abstinence.

7.9.2. Biochemical Testing

To assess sustained smoking abstinence for 6 months we require biochemical confirmation following self-report of abstinence. Those who self-report abstinence in the short assessments will be instructed to have their abstinence confirmed biochemically within 10 days and given instructions on the *Way to Health* platform about their nearest available testing facility and remuneration. Participants will also be told whether they need to complete a urine cotinine, urine anabasine, or serum carboxyhemoglobin test, dependent on whether or not they are currently using any NRTs or e-cigarettes, as below:

Urinary cotinine test: for participants not reporting the use of NRT or cigarettes. A urinary sample with cotinine < 20 ng/ml will be used to confirm cessation.

Urinary anabasine test: for participants reporting use of NRT or e-cigarettes, as cotinine tests cannot distinguish cigarette nicotine from replacement therapy nicotine. A urinary sample with anabasine < 3 ng/ml will be used to confirm cessation.

Serum carboxyhemoglobin test: for participants only using e-cigarettes and no other tobacco products who self-report quitting but have a positive urinary cotinine sample. These participants will be offered a second opportunity to confirm abstinence with a blood sample. A blood carboxyhemoglobin level of < 4% will be used to confirm cessation.

Due to the location of the participants in this trial and the difficulty for some more remote or elderly patients to come in for testing we will offer sample submission in two different ways. Participants will be encouraged to submit samples for biochemical confirmation of abstinence at their health system's labs or local Quest labs using instructions from *Way to Health*; however, we will also allow patients to arrange through *Way to Health* to submit samples using the Provant Health mobile service. Provant Health is a biometric screening company that collects samples in patients' homes and sends those samples to ARUP for processing. Participants will be informed that they will be reimbursed differential amounts for submitting the sample at home or at a lab, according to the fee structure below:

	Health System/Quest Lab		Mobile Service	
Biochemical test	1,3, 6 mths	12, 18 mths	1,3, 6 mths	12, 18 mths
Urinary cotinine	$50	$100	$20	$40
Urinary anabasine	$50	$100	$20	$40
Serum carboxyhemoglobin	$50	$100	$20	$40

7.9.3. Patient-Reported Outcomes (PRO) surveys

Participants will be asked to complete PRO surveys at 6 months and 12 months analogous to the baseline survey, excluding demographic questions. These surveys will ask about participants' self-reported motivation to quit, self-efficacy related to cessation efforts, urge to smoke, perceived barriers to cessation, anxiety, health-related quality of life, and temporal discounting. We will additionally ask

participants' about their use of other pharmacologic or behavioral programs (e.g., smoking cessation programs, therapy sessions, hypnosis, group classes, herbs, books, etc.). Participants will be asked to self-report their lung cancer scan results.

8. Data Management

8.1 Data Collection

All research data will be captured electronically via the EHR and the NIH-supported *Way to Health* web platform (RC2-AG036592). All four health systems using the same EHR platform, EPIC, resulting in programming efficiencies for data builds and data extraction. *Way to Health* is an integrated, cloud-based platform that will substantially increase the efficiency of patient enrollment and tracking, data management, and financial disbursements. Senior *Way to Health* personnel provide managerial infrastructure specifically designed to provide all of the data management services.

8.2 Data Management

Patients' register their name and contact information (email, phone, mailing address) on the HIPAA-compliant *Way to Health* website so that they can be contacted longitudinally (see § 7.9 Longitudinal Assessments). All patient-reported responses to surveys and assessments will be linked to each participant by a unique *Way to Health* user ID number.

Data access groups will be set up in *Way to Health* that restrict study team members at other health systems from accessing PHI of patients outside their own health system. As the prime site, Penn study team will have access to all contact information of patients registered in *Way to Health* from across the four health systems in order to coordinate delivery of cessation aids, CVS vouchers, emails and two-way texts to study participants according to the study schedule, and study payments. Access to all the study data will be limited to specifically designated researchers who are responsible for contacting participants for follow-ups and responding to questions and concerns from participants. All research staff accessing *Way to Health* Data Security Agreement upon initial login to the platform.

Biochemical test results collected at health system labs, Quest labs, or via Provant Health mobile service or ARUP processing service will be integrated into *Way to Health* using unique patient identifiers. These entities will send monthly csv.files containing biochemical test results and patient ID through a secure file transfer protocol (sFTP) to the Penn study team for integration into *Way to Health.* The *Way to Health* platform has an established lab result feature for easy integration of these test results. Participants receiving financial incentives in Arm 4 will be requested to submit their social security number if they are to receive payments above the cumulative annual threshold of $600. Social security numbers will be transmitted in encrypted format to University of Pennsylvania's Accounts Payable, which will store the data for W-9 forms. After the social security numbers are no longer needed for disbursements, they will be deleted from our system.

Way to Health study data will also be linked to additional health information, such as LDCT results or number of prior lung cancer screens, emanating from the health systems' EHRs. Patient identifiers such

as name, DOB, and date of screening visit will be used to accomplish the EHR linkage. At Penn, this linkage will be undertaken by Penn study team members. At the other three health systems, however, this linkage to EHR-based data will be undertaken by the study team members at their respective institutions. At the end of the study, these study team members will create final analytic "limited datasets" (absent patient identifiers and the *Way to Health* study identifier) that will then be securely transferred via a secure file transfer protocol (sFTP) from the other three health systems to Penn and stored securely (see §8.3. Data Security).

8.3. Data Monitoring

The *Way to Health* platform is able to collect metadata on participants' engagement with the platform to be able to track engagement with the interventions. For example, *Way to Health* can capture the type of, and date when, NRT modalities (gum, patch, lozenge) were ordered, dates that co-payment vouchers were requested, information on the delivery of emails and text messages as well as capturing verbatim responses to all delivered text messages. By this means, the study will be able to capture adherence to the EFT mobile application and participants' interactions with EFT cues over a six-month period.

8.4. Data Security

An additional level of protection against research risks entails a series of data security elements that ensure the maintenance of confidentiality of all study data and participant information. The Data Coordinating Center will reside at Penn. The *Way to Health* system has a set of governing policies to ensure strict maintenance of all study data, including protected health information (PHI). These policies, in full. Can be accessed at: https://policy.waytohealth.org/#17-data-integrity-policy

In brief, all *Way to Health* servers are managed by Penn Medicine Academic Compute Services (PMACS). These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. All data at-rest is stored on encrypted disks using encryption keys managed by *Way to Health*. Encrypted disks use AES encryption with a minimum of 256-bit keys, or keys and ciphers of equivalent or higher cryptographic strength. User passwords are never stored in clear text; they are "salted" and "hashed" to eliminate data leakage. All data transmission is encrypted end to end using encryption keys managed by *Way to Health*. Transmission encryption keys use a minimum of 2048-bit RSA keys, or keys and ciphers of equivalent or higher cryptographic strength (e.g., 256-bit AES session keys in the case of IPsec encryption).

Security is paramount. To monitor ongoing usage of the system and identify unauthorized usage of the system, all access to the application and the database are logged automatically. The *Way to Health* team perform regular (at least monthly) vulnerability scans of their systems to identify and patch any known vulnerabilities. They also run Intrusion Detection Systems (IDS) to identify unauthorized system access. *Way to Health* also has policies and procedures in place for system recovery following a disruption resulting from a disaster (such as extended outages). *Way to Health* has automated procedures to create and maintain retrievable data utilizing their Backup Service. These backup procedures are run on a daily basis and stored in a different location. Backups are encrypted. Backups are retained for a rolling

14 day period. Recovery from backups is also tested on a quarterly basis.

Data downloads are generally prohibited by *Way to Health* policy. Where appropriate, most datasets are blinded of all personally identifiable information when exported for analysis. A limited number of exports including identifiers exist to assist research staff with recruitment tracking and study management efforts. These datasets are only accessible to certain user roles. These user roles are required to sign and adhere to a *Way to Health* Security Agreement. The Way to Health data managers will formalize secure data protocols for transfer of *Way to Health* data to the PAIR Center's secure fire-walled server, with restricted access by PAIR Center's full-time data manager, Mr. Brian Bayes, and appropriate analytic staff. No study data will be stored on stand-alone

9. Analysis

9.1. Sample Size and Statistical Power Calculations

Based on our previous trials, and considering the population to be studied in the present trial, we anticipate a six-month prolonged abstinence rate of 2.5% with basic usual care. Although somewhat higher rates of cessation were observed in usual care during the National Lung Screening Trial, that trial used self-report to determine smoking status and enrolled patients who were interested in improving their health, rather than the non-selected patients to be enrolled in this pragmatic trial. We wish to detect absolute differences of at least 5 percentage points in abstinence rates between any of the three intervention arms and basic usual care or between any two of the three intervention arms (six total contrasts). This difference is clinically important given the dramatic health benefits of stopping smoking and the low rates of success of available interventions, and is identical to that used to determine power in our recent pragmatic RCTs.

Contrast	Health systems contributing data to the analysis
AAR vs. AAR + pharmacotherapy	3 health systems, excluding Kaiser
AAR vs. AAR + pharmacotherapy + EFT	3 health systems, excluding Kaiser
AAR vs. AAR + pharmacotherapy + EFT + incentives	3 health systems, excluding Kaiser
AAR + pharmacotherapy vs. AAR + pharmacotherapy + EFT	All 4 health systems
AAR + pharmacotherapy vs. AAR + pharmacotherapy + EFT + incentives	All 4 health systems
AAR + pharmacotherapy + EFT vs. AAR + pharmacotherapy + EFT + incentives	All 4 health systems

Because Kaiser will not enroll patients in basic usual care, we project enrollment of 470 patients in the basic usual care arm and of 910 patients in each of the three other arms, for a total of 3,200 patients. This sample and distribution will still yield >80% power to detect 5 percentage point differences in each of the six contrasts of interest, using the Holm method to adjust for multiple comparisons. The Holm method sequentially tests the significance of the six contrasts against progressively less restrictive alpha levels, preserving the familywise Type I error rate of 5%.

9.2. Statistical Analysis

9.2.1. Primary Analytic Approaches

We specify three sets of inferential analyses. First, our primary analytic approach will be to conduct intention-to-treat (ITT) analyses using logistic regression to compare the overall effectiveness of the interventions in achieving sustained abstinence among all randomized participants. The ITT analysis provides an unbiased test of the overall effectiveness of the interventions. However, this approach does not evaluate the effects of using the different interventions, because the effect sizes it yields will be diluted by the fact that some randomized patients will not use the interventions offered to them. Specifically, some patients referred by their clinicians to smoking cessation behavioral counseling, offered free cessation aids, and/or offered the mobile health application will choose not to use these interventions. Additionally, some patients offered incentives will not agree to provide their Social Security Number, as is required for tax purposes. Thus, our second analysis will use logistic regression to compare rates of intervention uptake based on the foregoing metrics. Third, we will compare interventions' efficacy by using a two-stage residual inclusion model in which the randomization arm is used as an instrumental variable in complier average treatment effect analyses. Such analyses use data on all randomized participants to provide unbiased estimates of the effects of using the interventions, after accounting for differences in uptake rates across arms.

All analyses will be conducted with adjustment for the pre-specified, patient-level, baseline covariates as well as fixed effects for clinic to account for unobserved characteristics common to patients in a given clinic. All analyses will include fixed effect terms for health system, thereby both preventing confounding by system and appropriately adjusting variance estimates to account for potential similarities among patients within a given system. In sensitivity analyses, we will only include health system and clinic fixed effects without patient-level covariates.

9.2.2. Approach to Missing Data

We will follow all CONSORT reporting guidelines (www.equator-network.org). Statisticians blinded to trial arm will prepare reports describing all data using appropriate summary statistics with estimates of variance and graphical representations of the distributions. We will compare distributions of the characteristics of enrolled patients to those of all patients identified as potentially eligible to quantify the trial's external validity.

Our first step in handling missingness will be to report all reasons for data missingness in detailed CONSORT diagrams, as we have done in prior RCTs. Further, because there is no single optimal approach to handling such missing data, we will assess the potential impact of missing data on the results in two complementary ways to promote valid interpretation of our data. First, we will conduct secondary analyses using multiple imputation to address missing outcomes. This approach allows use of baseline and available follow-up data (e.g., at baseline and 6 months) to inform the generation of values for subsequent missing data points (e.g., at 12 months), and properly adjusts for the uncertainty in the resulting imputed values. Second, we will conduct sensitivity analyses using pattern-mixtures models to explore and potentially adjust for patterns of missingness.

9.2.3. Heterogeneity of Treatment Effects

We will test statistical interactions between pre-selected patient characteristics and each contrast between two interventions in logistic regression models to guide future targeting of optimal interventions for individual patients. We will evaluate each interaction term separately in a model adjusted for all main effects and clinic to estimate stratum-specific effects of each characteristic on the interventions' effectiveness. We will also report results from a fully adjusted model that retains all significant interaction terms. Achieving the target sample size will provide >80% power to detect differences of at least 10 percentage points for statistical interactions between the comparative effects of two interventions and dichotomous patient characteristics (e.g., black vs. white) in which the less commonly observed characteristic is represented among at least 25% of participants. This calculation of power to detect statistical interactions uses an alpha level of 0.10, as in our prior study of modifiers of the effects of smoking cessation interventions. We will limit our search for heterogeneity of treatment effects to variables selected based on *a priori* hypotheses. Our preliminary list of effect modifiers are: demographics, tobacco dependence, smoking history assessment, temporal discounting, low-dose screening CT results, number of prior lung cancer screens, social acceptance of cessation efforts, presence of pharmacologic or behavioral programs, and presence of chronic smoking-related illnesses.

10. Oversight

10.1. Regulatory Approvals

The University of Pennsylvania IRB (IRB00009947) will serve as the central IRB of record for this trial. This single-IRB approach is now required for new grants for multicenter clinical trials to the National Institutes of Health, and we believe it is appropriate for this proposed trial as well. We will execute reliance agreements with the IRBs at Geisinger (IRB00008345), Henry Ford (IRB00000253), and Kaiser (IRB00000403). After IRB approvals, we will register the trial at ClinicalTrials.gov prior to enrollment of the first participant and submit clinical trial results to ClinicalTrials.gov within 12 months from the primary completion date.

10.2. Data and Safety Monitoring Board

To guide the safe and ethical conduct of this study, we have assembled a Data and Safety Monitoring Board (DSMB) with requisite expertise in lung cancer screening, smoking cessation, biostatistics, and the administration of programs to reduce smoking. The DSMB will be chaired by Renda Wiener, MD, MS, an expert in lung cancer screening and smoking cessation at Boston University. Other DSMB members will be Christopher Slatore, MD, another expert in lung cancer screening and smoking cessation at Oregon Health Sciences University, Joelle Fathi, DNP, a nurse practitioner with expertise in leading smoking cessation programs for older smokers, and Scott Evans, PhD, Professor and Director of the Biostatistics Center at George Washington University School of Public Health, and Dr. Neil Dickert, MD PhD, Assistant Professor of Medicine at Emory University School of Medicine. Dr. Dickert is an internationally recognized authority on research ethics, with particular expertise in the ethics of payments for research participation and alternatives to traditional informed consent.

The DSMB is primarily responsible for safeguarding the interests of trial participants, assessing the safety of the intervention during and at the end of the trial, and for monitoring the overall conduct of the clinical trial to assess the overall-risk benefit ratio of the intervention. The DSMB will be responsible for deciding whether to continue or terminate the trial based on patient safety. The DSMB may also determine whether amendments to the protocol or changes in study conduct are required in order to protect human subjects. Members of the DSMB will not be involved in the conduct of the trial.

Once convened, the DSMB will perform several duties. First, they will meet in the year prior to the study's implementation to review and approve the DSMB Charter, statistical analysis plan, research protocol, and plans for ongoing data and safety monitoring. As part of this initial meeting they will also determine the schedule for interim analyses and regularity of DSMB meetings (at least annually). Second, they will assess patient safety data and evaluate participant risk versus benefit. Third, they will make recommendations to ensure that any identified issues are appropriately addressed. The DSMB will make recommendations about study progress, safety, or trial continuation based on detection of any early evidence of harm. We do not plan to stop the trial early for evidence of effectiveness of the intervention because doing so would markedly reduce our power to detect heterogeneity of treatment effects – that is, which types of interventions best promote smoking cessation for which types of patients. We will propose to stop the trial (or a trial arm) early in the unlikely event that evidence arose of adverse effects of other types of measurable harm. Dr. Halpern (PI) will be directly responsible for identifying and reporting all serious adverse events, protocol deviations/violations and unanticipated events to the Penn IRB and DSMB.

10.3. Stakeholder Advisory Committee

The Stakeholder Advisory Committee was established during the grant proposal process and includes research partners that represent the broad impact of smoking among underserved patients: community and policy organizations, clinician and payer leaders, and patients. These stakeholders are focused on empowering underserved low-income, low-education, black, and/or Hispanic communities; promoting and implementing public health programs; and/or preventing tobacco-associated disease. Michael Scott of the National African American Tobacco Prevention Network serves as Lead Stakeholder Partner.

The SAC will operate throughout all years of the study to engage with the research team on study design, implementation, patient follow-up, analysis, and dissemination of study results. A SAC Charter was developed to help guide SAC roles and responsibilities, reimbursement, communication and meeting schedules, and committee expectations. The research team and SAC members will work as partners and uphold the principles of engagement that include: reciprocal relationships, partnerships, co-learning, and transparency, honesty, and trust. As such, partners will collaboratively identify agenda items for discussion, present key updates, and receive feedback throughout the course of the study. Broadly, SAC members will be asked to share opinions and strategies about how to best engage the patient population in the interventions throughout the course of the study; identify appropriate, patient-friendly ways to enroll patients in the study; advise the research team on how to scale up and implement smoking cessation strategies on the health system level; guide the research team in how to

make sense of and share the study results; develop new and creative ways to help others learn from our successes and challenges as research partners; and evaluate the research team's engagement plan to ensure that it aligns with the Committee's goals and expertise.

The SAC will meet in-person twice a year, supplemented by newsletters, phone calls as needed, and ad hoc meetings and workgroup email exchanges as stakeholders' availability and interests align. The goals of in-person meetings will be: 1) co-learning through educational sessions on successful research engagement and patient-centric research practices, including those led by SAC members,2) reviewing progress, including collaborative problem-solving for encountered or anticipated barriers, 3) establishing goals and delegating tasks for the subsequent year, and 4) forming closer relationships between the entire research team. All travel expenses will be covered, as will any hardware or software computer needs to facilitate participation and regular contact with research team members collaborating on work products.

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PROTOCOL AMENDMENTS LOG

Protocol Number: Penn IRB 833713

Protocol Title: Comparing Smoking Cessation Interventions among Underserved Patients Referred for Lung Cancer Screening: A Randomized Clinical Trial

Principal Investigator: Scott D. Halpern

The original protocol version was approved by the University of Pennsylvania IRB on November 22, 2019.

Concept: Trial duration
Date: Approved April 9, 2020
Summary: Removal of the 18-month Longitudinal Timepoint
Justification: Advice from our stakeholder advisory committee members was that engaging patients for 18 months was a more difficult task than promoting this study as a 12-month commitment. Other smoking cessation studies have not extended beyond 12 months previously and the investigative team did not believe there was a sufficiently compelling reason to include it in this study, given stakeholder concerns that it may adversely impact accrual rates.

Concept: Trial design
Date: Approved April 9, 2020
Summary: Addition of Study Site Lancaster General Hospital
Justification: As the lung cancer screening program at Lancaster General Hospital (LGH) is run separately from the lung cancer screening programs at Penn, LGH was added as it's own site. Dr. Scott Halpern will serve as the PI for both the Penn and LGH sites.

Concept: Trial design
Date: Approved April 9, 2020
Summary: Modifications to participant remuneration
Justification: Participants originally were to receive $50 for submitting each biochemical sample at 2 weeks, 3 months, and 6 months from target quit date, this is now modified such that participants receive $5 for completing the short assessment to determine whether or not they need a biochemical confirmation and up to $45 (depending on modality) for submitting a sample for biochemical confirmation. The same modification was made for the 12-month biochemical confirmation, splitting the $100 payment into a $5 payment for completing the short assessment and up to $95 (depending on modality) for submitting their sample for biochemical confirmation.

Concept: Trial design
Date: Approved April 9, 2020
Summary: Expansion of text-and email-based outreach facilitated by REDCap

Justification: Recruitment efforts will be supplemented with text-and email-based outreach. Lung cancer screening clinics are very busy, which would lead to a higher likelihood of eligible patients being missed by clinic staff.

Concept: Trial design
Date: Approved April 9, 2020
Summary: Biochemical confirmation for e-cigarette users
Justification: E-cigarette users will be directed to take a blood carboxyhemoglobin test rather than a urinary test to confirm abstinence from e-cigarettes.

Concept: Trial design
Date: Approved March 24, 2021
Summary: Smoking Cessation Oral Medications offered at reduced cost vs free
Justification: The original study design allowed participants in arms 2-4 to use a CVS voucher at the point-of-sale for purchasing FDA-approved pharmacotherapy. However, due to contractual and operational issues with the CVS Voucher system, this option was no longer viable. To reduce the financial burden of using FDA-approved pharmacotherapy, participants in arms 2-4 may request medication reimbursement of up to $300.

Concept: Patient-reported outcomes
Date: Approved March 24, 2021
Summary: Addition of Consumer Financial Bureau Protection (CFBP) financial wellbeing scale and other variables
Justification: The CFBP is a 5-item scale that assesses four substantial areas of financial wellbeing, namely control, capacity to absorb a shock, being on track to meet goals, and freedom of choice. Additional variables added include questions related to smoking history (e.g., past quit attempts, age at first smoking, use of e-cigarettes, nicotine replacement therapies, and other tobacco products).

Concept: Analysis
Date: Approved March 24, 2021
Summary: Addition of age, financial wellbeing, internet access, and comorbid illnesses to assess heterogeneity of effectiveness of treatment arms
Justification: The inclusion of these variables will provide a deeper understanding of the impact and effectiveness of the treatment arms across participant populations.

Concept: Eligibility criteria
Date: Approved July 01, 2021
Summary: Expansion of the number of cigarettes from 5 or more to 1 or more daily
Justification: This change was made to better align the clinical trial with methods used in other smoking cessation trials in which the criteria of “daily smoking” did not contain a minimum number of

cigarettes. This change came after discussion with the Stakeholder Advisory Committee of health system leaders and smoking cessation experts.

Concept: Secondary outcomes
Date: Approved July 01, 2021
Summary: Removal of nicotine dependence as a secondary outcome
Justification: Nicotine dependence is measured in the Fagerstrom survey, which will only be completed at baseline, and therefore, nicotine dependence is not a secondary outcome.

Concept: Enrollment process
Date: Approved March 04, 2022
Summary: Last chance to opt out
Justification: The mechanism of the opt-out consent process includes a technological inflexibility requiring participants to hit “continue”. This resulted in many participants being stuck, not opting out, and not hitting “continue” to be moved to enrollment. Under a true opt-out consent process, participants would automatically be moved to randomization. To address this matter, the last chance to opt out process was adopted, where participants who were stuck were messaged that they would automatically be moved to enrollment in 3 days unless they replied to the message to opt out.

Concept: Trial design
Date: Approved September 06, 2022
Summary: Lab results cut-off for confirmed quit
Justification: The cut-off for acceptable cotinine results for confirmed quit was expanded from <20 ng/ml to <=50ng/ml to prevent potential false positive results from kicking a participant off the quit path. Lab results with cotinine values of 20>50 are analyzed separately as potential false positives. Acceptable carboxyhemoglobin results for confirmed quit were changed from <4% to <=4% to address the fact that the lab reports only produce whole numbers.

Concept: Trial design
Date: Approved September 06, 2022
Summary: Availability of smoking cessation aids offered in arms 2-4
Justification: Smoking cessation aids and reimbursement for FDA-approved pharmacotherapy are available to all participants randomized to arms 2-4 beginning from enrollment through the target quit date. To address budgetary concerns, benefits remained available to this cohort through 6 months from the target quit date as long as the participant had biochemically confirmed abstinence.

Concept: Trial design
Date: Approved November 03, 2022
Summary: Additional messaging for Kaiser Permanente participants
Justification: Participants enrolled at Kaiser Permanente receive free cessation aid from their health system and therefore do not receive this benefit and related messaging through the study. Early analysis showed Kaiser participants reporting less use of nicotine replacement therapy (NRT) when

compared to participants enrolled at the other participating health systems. To address this, messaging to Kaiser Permanente participants was modified to include repeated messaging about accessing free NRT through their health system. The added messages better reflect messaging sent to participants in arms 2-4 of the other participating health systems in the study.

Concept: Eligibility criteria
Date: Approved November 03, 2022
Summary: Kaiser Permanente membership requirements for Kaiser Permanente participants
Justification: Patients recruited through Kaiser Permanente must also be members of Kaiser Permanente to be eligible for the study. This is to ensure (1) Kaiser Permanente participants have access to the Kaiser Permanente Wellness Coaching and free cessation aid resources, only available to Kaiser Permanente members; (2) the Kaiser Permanente team has access to the medical records of all enrolled participants at their health system and is able to share study-required electronic health system data.

Concept: Trial design
Date: Approved July 24, 2023
Summary: Clarification of the lab window
Justification: To be more participant-centered and aligned with being a pragmatic trial, when lab results are unavailable within the window due to reasons beyond the participant's control, lab results outside the 28-day window are acceptable. Those results are reviewed by the PI to determine if they meet the criteria for inclusion in the analysis.

Concept: Trial design
Date: Approved July 24, 2023
Summary: Ability to repeat a lab sample at the request of the participant
Justification: Under certain conditions, participants will be allowed to repeat a lab sample if they believe the results do not support the confirmed quit.

Concept: Analysis
Date: Approved September 22, 2025
Summary: Final modifications to the Statistical Analysis Plan incorporated into the study protocol
Justification: Certain elements of the Statistical Analysis Plan (SAP) were modified post-hoc. These modifications are outlined in the SAP amendment log. The IRB approved these edits in July; however, the protocol itself was not included in that modification. This modification included those approved edits as incorporated into the study protocol.