Social and Behavioral Sciences Human Research Protocol

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INTRODUCTION AND PURPOSE

Continued tobacco smoking negatively impacts survival among patients with cancer.[1-3] Routinely delivered evidence-based tobacco use treatment (TUT) would minimize cancer-specific and all-cause mortality, reduce treatment-related toxicity, and improve quality of life.[1] About 50% of cancer patients who smoked prior to their diagnosis continue to smoke after diagnosis and during treatment.[4] The National Comprehensive Cancer Network,[3] American Society of Clinical Oncology,[5] and American Association for Cancer Research,[6]call for implementation of TUT within oncology care. In 2015, TUT received an "A" recommendation from the US Preventive Services Task Force, given the high level of certainty of resulting benefit. The approval specifically focused on clinicians asking all adults about smoking, prescribing FDA-approved cessation medications for smokers, and offering appropriate behavioral interventions.[7]

Despite the importance of TUT, only half of cancer centers consistently identify patient tobacco use,[8] and few cancer centers employ systematic mechanisms to refer patients to evidence-based cessation services.[7] Acknowledging this gap, the National Cancer Institute (NCI) launched the Cancer Center Cessation Initiative (C3I) as part of the Moonshot to help centers develop effective ways to identify and engage patients who smoke.[9] Penn ISC3 MPI Dr. Schnoll was a member of the NCI advisory board that developed this initiative, and Penn Medicine's Abramson Cancer Center (ACC) was in the first funded cohort.[9] Because clinician expertise in TUT is a known barrier,[10-12] our initial strategy used an automatic "default" electronic medical record (EMR) referral to the ACC Tobacco Use Treatment Service (TUTS). Engagement increased, but clinicians turned off the default 60% of the time, implicating additional important barriers to change.

This study aims to produce dramatic change within oncology by refining and testing implementation strategies informed by behavioral economics.[13-15] Our work has identified specific cognitive biases among clinicians and patients that prevent TUTS referral and engagement, including clinician pessimism regarding the ability to help patients stop using tobacco, misconceptions about patient resistance to treatment, and implicit biases regarding the capacity for patients to volitionally alter the course of illness.[16] These motivators are related to clinician willingness to invest effort in help giving[17-19] and may prevent acquisition of new knowledge and skills.[20] From the patient perspective, several studies identify unique challenges that individuals with cancer face when engaging in tobacco cessation efforts, including low self-efficacy, low perceived benefits of quitting, and perceived risk of treatment.[21-23] Thus, this study focuses on addressing these barriers, in a pragmatic and innovative way, to increase TUTS referral and engagement in cancer care.

Our objectives are to evaluate the effectiveness of "nudges" to clinicians, to patients, or to both in increasing in TUTS referral and engagement; and to explore clinician, patient, inner setting (e.g., clinic), and outer setting (e.g., payment structures) mechanisms related to TUTS referral and engagement. We will employ rapid-cycle approaches to optimize the framing of nudges to clinicians and patients prior to initiating the trial and mixed methods to explore contextual factors and mechanisms.

We will conduct this study with at least 100 clinicians and at least 900 smokers across Penn Medicine's ACC (the clinician sample size may increase with additional clinicians joining Penn and the patient sample size may be higher given the pragmatic design and delay between determination of eligibility [i.e., patient smokes] and nudge delivery at a subsequent visit). We

expect the study to yield essential insights into the effectiveness of nudges as an implementation strategy to speed the uptake of high value evidence-based TUT within cancer care, and to advance our understanding of the multilevel contextual factors that drive response to these strategies. These results will lay the foundation for how cancer care settings can ensure that patients with cancer who smoke are engaged with evidence-based TUT and may lead to a future R01 focused on scaling-up this approach across other cancer centers involved in the C3I.

OBJECTIVES

Aim 1: Conduct a four-arm pragmatic cluster RCT to test the effectiveness of nudges to clinicians, nudges to patients, or nudges to both in increasing TUTS referral and engagement in cancer patients who smoke, vs. usual care (UC). H1a: Each of the implementation strategy arms will significantly increase TUTS referral and engagement compared to UC. H1b: The combination of nudges to clinicians and to patients will be the most effective.

Aim 2: Conduct a quantitative evaluation using secondary data (obtained via EMR, for patients, and by survey, for clinicians) to identify moderators of implementation effects on TUTS referral and engagement. H2: Nudge impact will be moderated by clinician, patient, and inner setting factors. [Note: the clinician survey will be conducted within a separate study funded by this grant and submitted for IRB approval as a separate protocol; data across the studies will be linked by clinician name and study ID.)

Primary outcome variables:

In Aim 1, we will test optimized implementation strategies in a four-arm pragmatic cluster pilot RCT to test the effectiveness of nudges to clinicians, nudges to patients, or nudges to both in increasing TUTS referral and engagement in cancer patients who smoke, vs. usual care (UC – default referral only). Primary and secondary implementation and effectiveness outcomes, and contextual factors that shape implementation effectiveness, will be captured.

Secondary outcome variables:

In Aim 2, we will explore moderators of effectiveness by analyzing associations with variables available via the EMR and clinician survey.

BACKGROUND

In 2014, the US Surgeon General concluded that there is a causal relationship between cigarette smoking and adverse health outcomes in patients with cancer. Smoking adversely effects survival: it accelerates tumor growth and increases disease progression, tumor resistance to treatment, and treatment-related toxicities. [24-28] Quitting smoking improves prognosis. As cancer survival rates and durations have improved, with 15 million survivors of cancer in the US, the impact of continued cigarette smoke exposure has gained ever-increasing relevance.[1] Evidence-based TUT services are likely to have benefits for those currently in care,[1] as well as for the 2 million survivors who continue to smoke.

Tobacco Use Treatment is the new standard of care. In 2017, the NCI launched the *Cancer Center Cessation Initiative* (C3I) within the Moonshot Program.[9] Its goal is to help cancer centers build and implement sustainable TUT programs that can routinely provide evidence-based treatment to patients and improve patient outcomes. One of the major objectives of the C3I initiative is to evaluate and overcome clinician, patient, clinic, and health system barriers by fully integrating TUT into cancer care services. C3I focuses on clinical workflow management and minimizing treatment plan variability as they relate to TUT.

Initial efforts to implement universal screening and referral at Penn Medicine's ACC. Penn ISC3 MPI Robert Schnoll was integral to the efforts to formulate C3I, serving as a member of the NCI advisory board drafting and presenting the initiative to NCI leadership. ACC was in the first cohort of cancer centers selected for C3I. With this funding, the ACC's Tobacco Use Treatment Service (TUTS) was built by Penn ISC3 members Drs. Leone, Schnoll, Beidas, Shulman, and Gabriel, and Ms. Chen, based on the evidence-based *Ask-Advise-Connect* model.[30] This approach 1) systematically identifies smokers (Ask); 2) provides personal and persuasive advice to quit smoking (with attention to practical and emotional barriers; Advise); and 3) facilitates access to TUT, including counseling and FDA-approved medication through an EMR-based default (i.e., automatic referral; Connect). The approach involved standardizing a mandatory assessment of smoking status for all ACC patients, integrating cancer-relevant cessation advice in the written After Visit Summary, and building a fully automated electronic referral mechanism to Certified Tobacco Treatment Specialists that minimized disruption to workflow. Because the stressful dynamic of oncology practice may present additional barriers,[31] we built in a process evaluating the suitability of TUT for integration into oncology workflow.

Evaluation shows the implementation strategy was promising, with room for improvement. Since initiation about 1 year ago (~13,000 patients), rates of tobacco screening remain consistently at ~90%, suggesting that our approach has successfully accomplished near-universal tobacco use assessment. The prevalence of current tobacco smoking among ACC patients remains under 10%, suggesting overwhelming volume is not an obstacle to referral. Referral rates to TUTS over the 6 months prior to implementation were 0% (C3I required determination of these data to establish base rates), but rose to 34% across the 6 months following implementation, suggesting that clinician behavior changed.[32] Focus group data suggest oncologists accept the professional role and social responsibility of monitoring tobacco use, and that TUTS effectively reduced workflow burdens and eliminated practical barriers to engagement. Nonetheless, clinician referral to TUTS remain highly variable; individual referral rates range from 0% to 100%. High rates of order cancellation (i.e. "opting out" of the default referral) emerged as an important barrier to achieving our goal that all clinicians consistently make TUTS referrals. Subsequent efforts to address this issue, including additional education and leadership encouragement (ACC Director and Medical and Radiation Oncology Division Chairs endorsing TUTS at faculty meeting), reduced opt out rates, yet there remains sizable room for improvement. Work in other areas, such as generic medication prescribing in internal medicine practice, suggests that system changes that use a "default" to target clinical behaviors may have an impact on treatment rates but additional work is needed to overcome clinician biases and help patients engage in treatment.[33] Although our simple pragmatic workflow change moved the needle, the next step is to augment the current approach with additional insights from behavioral economics.[34]

Additional research has identified targets for intervention. For several years, our group has been engaged in applying insights from behavioral economics to understand physician biases around TUT. Findings from preliminary work examining physician preferences toward TUT

revealed a strong preference for interventions perceived to be effective. This finding led us to examine the role of clinician biases regarding treatment success probabilities under conditions of uncertainty.[35] We showed that strategies minimizing well-established cognitive biases (i.e., *availability bias* [the tendency to be influenced by recent or common examples], *omission bias* [the tendency to focus on the potential harm of action more than that of inaction], *impact bias* [the tendency to overestimate the emotional impact of an event] and *focusing effect bias* [the tendency to focus on a selected detail rather than the big picture]) are more successful at changing physician behavior than strategies that solely aim to increase knowledge of TUT service availability.[36] Most recently, our group has identified an implicit association between smoking status and a culpability theme that appears to influence both the emotional characteristics of clinician-smoker interactions and clinician willingness to invest effort in treating tobacco use.[37] At the same time, specific biases exhibited by those with cancer can reduce engagement in TUT, including *status quo bias* (tending to stick with a current choice even if better alternatives exist),[38] *present bias* (the tendency to give more weight to current or near-future benefits or costs than to longer-term benefits and costs),[39] *focusing effect bias*, and *availability bias*.[35] Thus, complex and overlapping behavioral economic constructs play a significant role in determining referral and engagement decision-making and targeting these constructs could significantly improve upon the model we have built at the ACC.
This study will be the first in the oncology setting to compare effectiveness of nudges to clinicians and patients, both head-to-head and in combination, as implementation strategies to improve TUTS referral and engagement. It builds upon our prior work and targets biases among both clinicians and patients, addressing known barriers to tobacco cessation in this high-risk population. The intervention will be embedded within the EMR and clinician-directed nudges will be designed to minimize interference with established workflow while incorporating attention to the motivation needed to make behavior changes.[38] This trial will be conducted across the Implementation Laboratory, including both urban and non-urban sites. Finally, the study shares the innovative elements described elsewhere in this application: the use of rapid-cycle approaches to refine the implementation strategies to be tested and the use of mixed methods approaches to enable new insight into context and mechanisms that underlie effectiveness, scalability, and generalizability to other clinical problems and populations.

CHARACTERISTICS OF THE STUDY POPULATION:

1. Target Population and Accrual:

Recruitment will include projected subject recruitment totals of at least 100 clinicians and at least 900 smokers at 9 sites across Penn Medicine's ACC. The target population includes approximately 2,300 high-risk patients with cancer cared for by approximately 275 medical and gynecologic oncology clinicians at the following hospital and free-standing community practice sites of the Penn Medicine Abramson Cancer Center (ACC), referred to hereafter as the "Implementation Laboratory": Hospital of the University of Pennsylvania (HUP), Pennsylvania Hospital (PAH), Penn Presbyterian Medical Center (PPMC), Chester County Hospital (CCH), Lancaster General Hospital (LGH), Valley Forge Medical Center, Radnor Medical Center, Cherry Hill Medical Center, Voorhees Medical Center, Sewell Medical Center, and Regional Hematology Oncology Associates. The trial will be conducted pragmatically, and patients will accrue as they are seen in follow-up at a participating practice site by an eligible provider; this approach may result in a sample of patient that exceeds 900.

2. Key Eligibility Criteria:

Clinician participants must meet the following criteria for enrollment:

1) Currently in practice at an Implementation Lab site (UPHS)
2) Prescribing authority in Pennsylvania (i.e., physician, nurse practitioner, physician assistant)
3) Cared for at least 1 tobacco-using patient in 30 days prior to recruitment
4) English-speaking (messages will be in English)

Patient participants must be diagnosed with cancer and report current tobacco smoking (as assessed by any staff collecting vital signs or initially rooming the patients such as nurses, front desk staff, MAs, nursing assistants or technicians during an Index Visit). Patients are considered in the analyzable dataset after their Index Visit and after they have a clinic visit with a clinician in the study at which point a nudge may have been delivered (see steps below).

The process by which patients become eligible for inclusion involves a 3-step algorithm employed in the EMR:

- Step 1 – All patients seeking care within the participating Abramson Cancer Center programs are screened for tobacco use status in order to ascertain relevance to the project (i.e., tobacco exposure). This screening encounter need not be a visit with a clinician who is in the cluster randomization.
- Step 2 – This step occurs at the first visit with a clinician within the cluster randomization. Note that this might be the same encounter in which screening occurs, but does not have to be. At this visit, all patients identified as current smokers are assigned a hidden (i.e., system) variable, the value of which is based on the clinician they are scheduled to meet during that visit (i.e., cluster membership).
- Step 3 – The logic is engaged at the next (third in series) visit, wherein the system variable is used to guide the intervention based on the clinician's cohort. There must be this visit to permit the delivery of the nudges (or not, if in usual care arm). The primary outcome is clinician referral for tobacco cessation through the EHR at this visit. Thus, patients eligible for this study are only those who are screened (and positive for tobacco use) and have completed the two visits in their randomly assigned cluster (clinician clusters are the unit of randomization) during the study period.

3. Subject Recruitment and Screening:

Drs. Leone and Jenssen have evaluated Clinical Decision Support Tools for promoting the treatment of tobacco dependence in Penn primary care and CHOP practices, respectively. As noted in A.3., we will seek a waiver of informed consent. Aim 2 will not require additional participants; it will include data from all clinicians randomized to the RCT, as well as patient-level EMR data for all patients treated by the clinicians in the sample set during the study period. The trial is pragmatic in nature, assessing the impact of implementation strategies delivered to clinicians and patients through minor adjustments to existing workflow delivered through the electronic medical record (EMR). Changes to workflow are by necessity systematically applied to all clinicians within the practices, as well as their patients. We will obtain a waiver of informed consent for clinicians and patients for pragmatic trial activities accomplished for Aims 1 & 2.

We view this project as a quality improvement initiative (with data collection to allow for corresponding evaluations of the initiative). As a result, the changes introduced to the EHR (i.e., nudges to promote tobacco use treatment referral and engagement) will be considered standard of practice within the healthcare system, thereby allowing for a waiver of informed consent for both clinicians and patients. It is important to note that clinicians and patients involved in the project will not be assigned a change in treatment; clinicians are still free to refer or prescribe, or

not refer or not prescribe, as they see fit. Instead, they are being reminded of an evidence-based practice (EBP) guideline and offered an opportunity to review pertinent information and refer to and/or prescribe the EBP (or not) as clinically appropriate. Thus, the implementation strategies offer minimal risk to clinicians and patients. This approach to informed consent and data collection will also aid implementation integrity and generalizability by avoiding behavior changes related to being observed (i.e., the Hawthorne effect). In other words, this initiative could not practicably be carried out without the waiver as obtaining consent would introduce significant bias into the work, preventing the ability to achieve the aims and achieve the study goal: improving evidence-based tobacco use treatment within cancer care. We see this study as similar to those which have received waivers from our Institutional Review Board before.[40,41]

4. Early Withdrawal of Subjects:

We are requesting a waiver of informed consent, so the option to early withdraw from this study is not applicable for Aims 1 and 2 of this project.

5. Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not being targeted in this research study.

6. Populations vulnerable to undue influence or coercion:

We will not be targeting participants who are likely to be vulnerable to undue influence or coercion. Clinicians employed by Penn may experience undue influence to take part in this study and, as outlined in https://irb.upenn.edu/sites/default/files/IRB%20SOP%20V.11.1-06.2019-Clean.pdf, efforts are needed to prevent against this potential. To this end, we will send a formal general notification to all clinicians regarding the proposed study, indicating that it will involve data ascertainment from the EHR, that they can opt out, and that decision to opt out will be confidential.

STUDY DESIGN

Aim 1. We will test optimized implementation strategies in a four-arm pragmatic cluster pilot RCT to test the effectiveness of nudges to clinicians, nudges to patients, or nudges to both in increasing TUTS referral and engagement in cancer patients who smoke, vs. usual care (UC – default referral only). Primary and secondary implementation and effectiveness outcomes, and contextual factors that shape implementation effectiveness, will be captured.

Aim 2. We will explore moderators of effectiveness by analyzing associations with variables available via the EMR and clinician survey.

Study Duration:

The exposure period will be 6 months for all participants, with a 90-day follow-up period to measure persistence of effects after implementation strategies end. The baseline period will be 3 months in length, permitting use of rapid cycle approaches (RCA; meetings with co-investigators David Asch and Allison Buttenheim and administrators and clinicians within the

Implementation Lab to refine nudges) during this period to optimize implementation strategies. Study analyses will proceed after the follow-up period has completed.

METHODS

1. Study Measures:

The Aim 1 primary measure of implementation is penetration (TUTS referral rate), defined as the number of TUTS orders signed, divided by the total number of pended orders (i.e., 1-cancellation rate). Our secondary measures of implementation include: prescription rate, defined as the number of pended orders accompanied by a signed prescription order for any of the seven FDA-approved medications for tobacco cessation, divided by the total number of pended orders; treatment engagement rates (medication), defined as the number of patients who make a pharmacologically-assisted quit attempt using any of the seven pharmacotherapies within 90 days of the initial oncology visit, divided by the total number of referred patients; treatment engagement rate (behavioral), defined as the number of patients who receive a quit-line referral or in-person or telephone cessation counseling, divided by the total number of TUTS-engaged patients; quit attempt rate, defined as the number of TUTS-referred patients who make any quit attempt, divided by the total number of TUTS-referred patients; and abstinence rate, defined as the total number of TUTS-referred patients self-reporting 7-day point prevalence abstinence at a 90-day follow-up assessment, divided by the total number of TUTS-referred patients. Established guidelines state that real-world pragmatic, population-based trials such as this do not require biochemical verification of abstinence and including it could introduce significant bias.[42] Note, we will continue to monitor assessment rate (defined as the number of times the BPA is answered divided by the total number of times it fires) to ensure the intervention does not negatively impact assessment of tobacco use status by staff collecting vital signs or initially rooming the patients such as nurses, front desk staff, MAs, nursing assistants or technicians(baseline rate=90%).

Aim 2 measures, collected through the EMR, will include patient age, sex, race/ethnicity, type of health insurance (e.g., Medicare, Medicaid, Commercial), address, cancer type, and history of prior tobacco cessation pharmacotherapy. Clinician-level data will be collected by survey led by a separate study funded by this grant and approved by the IRB: site, years in practice, patient panel size, the prevalence of patient smoking in the patient panel, and type of oncologist (medical, radiation, surgical). Additional data will include practice-level data: setting (community vs. hospital-based), urban vs. non-urban location, and health insurance mix.

2. Administration of Surveys and/or Process:

Aim 1. No surveys will be administered as part of this study.
Aim 2. Any surveys used as part of this aim will be submitted to the IRB under a separate study protocol prior to use.

3. Data Management:

To minimize the risk of breach of data and confidentiality, we will use secure, encrypted servers to host the data and conduct the analysis. The Digital Academic Research Transformation (DART will be the hub for the hardware and database infrastructure that will support the project. DART provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. DART requires all users of

data or applications on DART servers to complete a DART-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations. Data will be stored, managed, and analyzed on a secure, encrypted server behind the University of Pennsylvania Health System (UPHS) firewall. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and the CITI human subjects research. Data access will be password protected. Whenever possible, data will be deidentified for analysis.

4. Subject Follow-up:

Patients who are referred to the TUTS program will be contacted by telephone 90 days after the subsequent visit to measure persistence of effects after implementation strategies end (e.g., self-reported tobacco use, quit attempts, use of cessation treatments).

STUDY PROCEDURES:

6. Detailed Description:

In Aim 1, we will test optimized implementation strategies in a four-arm pragmatic cluster pilot RCT to test the effectiveness of nudges to clinicians, nudges to patients, or nudges to both in increasing TUTS referral and engagement in cancer patients who smoke, vs. usual care (UC – default referral only). Primary and secondary implementation and effectiveness outcomes, and contextual factors that shape implementation effectiveness, will be captured. In Aim 2, we will explore moderators of effectiveness by analyzing associations with variables available via EMR, and by survey from a separate protocol supported by this grant.

This is a pragmatic clinical trial focused on increasing use of TUTS. In all arms, clinicians can still choose what they like and patients can still decide to engage in TUTS or not. We will seek a waiver of informed consent for clinicians and patients. We will identify clinicians at the practice sites and their patients using the EMR. Patients will be required to meet the above outlined eligibility criteria. Clinicians (i.e., the unit of randomization) within each site will be randomized to four arms using variable permuted blocks. To control for confounding due to the fact that a small number of clinicians may potentially treat patients at multiple sites, clinicians will be randomized to arm irrespective of site.

We will use RCA to optimize implementation strategies to ensure face validity and maximum effect. We will focus on optimizing content, messaging, and design. RCA procedures involve design meetings with David Asch and Allison Buttenheim and with discussions with administrators and clinicians who are members of our Implementation Lab. Clinicians and patients will be exposed to implementation strategies based on their assigned arm.

2. Study Intervention Phase:

Nudges to Clinicians. We will use the Best Practice Alert functionality within the EMR as our conduit to the point of decision-making. All sites use Epic (Epic Systems Corporation, Verona,

WI) to deliver care, or an interoperable system. Epic BPA deployment is modifiable, as we have done at the ACC (CA016520-41S4) and in primary care (DA045244). Epic currently "fires" a BPA for each new patient presenting to ACC within the check-in and vital sign workflow, requiring that staff collecting vital signs or initially rooming the patients such as nurses, front desk staff, Mas, nursing assistants or technicians assess tobacco use status within the past 30 days and satisfy the alert with one of three possible answers (CA016520-41S4). They then activate the "Order" tab for all patients identified as current smokers (i.e., within the past 30 days), resulting in placement of a pended order for consult to TUTS within the clinical workflow.

We seek to improve TUTS referral and engagement by overlaying normative framed messages to address clinician and patient biases. Upon opening the Epic Order tab at a patient's next visit after the screening encounter, clinicians will receive the implementation strategy, placed directly over the order interface. The clinician will be required to "acknowledge" or "opt-out" when presented with the order. Opting-out will require clinicians to acknowledge a reason for opt-out using a checklist or free text.

Nudges to Patients. Patients will receive a message sent through myPennMedicine following establishment of their smoking status (at the screening encounter). In all cases, the message will include information specific to the upcoming appointment with the oncology clinician.

Nudges to both clinicians and patients. Both strategies described above will be used.
Usual care. Clinicians and patients will receive no further interventions beyond usual practice. In early 2019, all Penn Medicine ACC clinicians receive the opportunity to refer to TUTS without nudges.

Message design and testing. Messages will be framed to undermine biases. We will optimize the framing of the messages using rapid-cycle approaches to ensure face validity and maximum effect

3. Data Collection:

The EMR and other Penn Medicine secondary databases (the TUTS program) will be used to collect information on practices, clinicians, and patients. These systems are used to routinely collect this information for patient care. We will also collect data from the census via publicly available datasets. Once collected, data are maintained on password-protected computers. Ms. Ware, who directs the PENN DMS, will oversee the DMS for this study. ORACLE and MS ACCESS permit real-time data entry, storage, and QA by web-based remote access and scannable forms which increases standardization across personnel. We have >15 years of experience with this DMS for smoking cessation trials. The DMS generates database tables, constructs semantic constraints on fields, and is used for data entry, storage, retrieval, and security. The DMS uses visit dates to describe procedures and measures to be ascertained. The DMS mimics the appearance of CRFs which are completed at each visit. Each visit date is "milestoned" (e.g., completed, scheduled, missed). Clinician data will be ascertained by a survey conducted under a separate IRB protocol and funded by this grant.

4. Genetic Testing:

n/a

5. Use of Deception:

n/a

6. Statistical Analysis:

Based on our preliminary data, we anticipate including at least 900 smoking patients (based on prevalence estimate of ~7% among 13,000 patients screened over a 1-year study period), nested within at least 100 clinicians. Analysis will use the first TUTS order generated for each patient/physician combination. Data are clustered within clinician, and the exchangeable correlation observed from other studies is small (0.07). We calculated power requirements by simulation using Stata 15, assuming a logistic regression model fitted using generalized estimating equations (GEE), and found our sample gives us 80% power to detect 11% improvement in our primary outcome (e.g., from current 34% referral rate to 45%), using a two-sided type 1 error rate of 5%, for planned comparisons between usual care and each individual nudge arm. The effect of the combined nudge arm is expected to be larger than each individually, indicating at least 80% power to detect probable effects for the comparison between usual care and the combined arm.

We have defined our intention to treat (ITT) sample using the coding algorithm that makes intervention possible, irrespective of whether a nudge was delivered or received. Thus, the ITT cohort is comprised of all eligible patients, defined as those who screened positive for tobacco exposure and have completed the two visits in their randomly assigned cluster. Eligible patients may or may not receive the nudge to which they were assigned and may or may not have access to MyPennMedicine; regardless, all eligible patients are analyzed in the ITT sample.

We have patient-level data on all those screened positive for tobacco but who did not complete the subsequent visits with a clinician in our cluster randomization (e.g., patient came for the first visit where the hidden system variable was assigned and never returned). While these patients are not considered eligible for our trial, they are part of the “screened” population, and we can compare them to our eligible patients on available data to assess the generalizability of our sample.

For Aim 1, we will analyze all binary outcomes using logistic regression with GEE. The study design is factorial, and models will contain binary predictor terms for clinician and/or patient prompt. We will conduct stratified analyses by MPM access. We will also include adjustments for time in months, fixed effects for site, and random effects for clinician. We will control for type 1 error inflation by hierarchical testing, starting with the overall model significance, followed by effect of clinician prompting, followed by patient prompting. Once we have fitted the main effects model, we will test for interaction between clinician and patient prompts, and retain that interaction term if significant (alpha=5%). For Aim 2, variability in these outcomes by treatment arm and moderators will be assessed using interaction terms within logistic regression models. We will fit an adjusted logistic regression model using the same approach described in the primary analysis. Covariates of interest available through the EMR and clinician survey will be added to the model, including patient-level (e.g., cancer type), clinician-level (e.g., years in practice), practice-level (e.g., community vs. hospital-based), and ecological data.

RISK/BENEFIT ASSESSMENT:

1. Risks:

There are minimal risks to participants in this trial. Regardless of nudges, treatment provided is FDA approved, clinicians routinely order treatment as part of their standard of care, and patients routinely use these smoking cessation treatments. The interventions could increase the time spent discussing smoking cessation with patients. However, shared-decision making is a high priority and evidence-based practice for cancer care and increased time on this topic is likely valuable. In our prior studies, nudges in the EMR were associated with minimal burden on practice staff and clinicians. There is a risk of breach of data and confidentiality, however we described the precautions in place to securely manage this data in the "Data Management" section of this protocol.

2. Benefits:

Clinicians and patients will receive no direct benefits from participating in this study. Participants who enroll in this trial will benefit from the knowledge that they are contributing in an important way to potentially furthering scientific knowledge concerning ways to improve evidence-based practice. The knowledge gained on how to increase evidence-based practice could be applied to other populations and implemented at other health systems. Patients may benefit from being more likely to receive evidence-based smoking cessation treatment and thereby more likely to quit smoking.

3. Subject Privacy:

Privacy will be given utmost consideration and is highly valued in the proposed research. No research activities involve any direct interaction with subjects that would pose risk to their privacy.

4. Subject Confidentiality:

Confidentiality refers to the subject's understanding of, and agreement to, the ways in which identifiable information will be stored and shared.

How will confidentiality of data be maintained? Check all that apply.

☐ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
☒ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
☒ Whenever feasible, identifiers will be removed from study-related information.
☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☒ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☒ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

☐ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

☐ Other (specify):

To protect participant confidentiality, only the research team outlined in HSERA will have access to review identified research records. Confidentiality will be protected to the fullest extent allowable under the law. See the Data Management section for more details.

If any data needs to be transmitted, it will be done through a Penn-approved secure encrypted file transfer solution as is described Penn IRB's Guidance on Electronic Data Protection Requirements for Research Involving the Use of PHI. Records will not be released without the participant's consent unless required by law (e.g., imminent risk of harm to self suspected) or court order. When results of the research are presented at scientific meetings or published, no identifying information will be included.

All identifiable data, including the master list linking identifiers to the ID number and recordings, will be destroyed in 2028, seven years after the award period ends.

5. Protected Health Information

- Name
- Address
- Date of birth
- Phone number(s)
- Medical record number
- Type of health insurance
- Cancer history
- Tobacco use and tobacco cessation history
- Electronic mail address

6. Compensation:

Aims 1 & 2. Participants will not be compensated for participating.

7. Data and Safety Monitoring Board:

The nature of the project poses minimal risk to participant safety and privacy. Yet, we will constitute a formal Data Safety Monitoring Board. The specific aspects of the DSMB for this study are as follows:

1. The DSMB will consist of 4 members: 1) Erin Aakhus, MD, Assistant Professor of Clinical Medicine, Perelman School of Medicine, University of Pennsylvania, Associate Director of the Hematology Oncology Fellowship Program 2) Kate Courtright, MD, MSHP, Assistant Professor of Clinical Medicine at the Perelman School of Medicine of the University of Pennsylvania 3) Kit Delgado, MD, MS, Assistant Professor of Emergency Medicine at the Perelman School of Medicine of the University of Pennsylvania, Associate Director of Center for Health Incentives and Behavioral Economics 4) Meghan Lane-Fall, MD, MSHP, David E. Longnecker Associate Professor of Anesthesiology and Critical Care & Associate Professor of Epidemiology at the Perelman School of Medicine of the

University of Pennsylvania, Associate Director of the Center for Health Incentives and Behavioral Economics

2. The DSMB will perform several duties. First, they will review and approve research protocols and plans for data and safety monitoring prior to any study commencement. Second, they will evaluate the progress of any eligible trial. This will include assessment of data quality, participant recruitment, accrual and retention, participant risk versus benefit, and study outcomes. This assessment will be performed at meetings every six months during eligible trials and, more frequently, if decided by the DSMB. Third, they will make recommendations to ensure that all of the issues above are appropriately addressed. The corresponding project teams will be responsible for responding to all recommendations of the DSMB and submitting DSMB reports to the University of Pennsylvania IRB.

8. Data and Safety Monitoring Plan:

Oversight and evaluation will be accomplished using standard University procedures for safety monitoring. The specific elements of our oversight plan are as above: 1) all project staff will complete certification in the protection of research participants; 2) the principal investigator will supply the IRB with annual progress reports prepared for CURE as specified, or more frequently as determined by the IRB, which may in turn suspend, terminate or restrict the study as appropriate; 3) any serious adverse events will be reviewed in real time by the PI and reported to the IRB as required; and 4) the PI will inform CURE reviewers of any oversight actions taken by the IRB. The data and safety monitoring plan will have 3 parts. First, the study MPIs, biostatistician, and Director of the Data Management Unit will develop and implement methods of verifying entered data and of quality control. Second, the MPIs will be directly responsible for identifying and reporting all adverse events, protocol deviations/violations and unanticipated events to the IRB and funding agency promptly, as appropriate. The PIs will also report all adverse events, accrual rates, retention rates, and all other logistical issues to the DSMB (described above) at least biannually (and more frequently if there are serious adverse events). Third, there will be a DSMB responsible for monitoring the trial.

A written research protocol will undergo formal institutional scientific and institutional review board (IRB) review at the University of Pennsylvania (Penn) to ensure protection of the rights and welfare of human research subjects. Specifically, the MPIs and the IRB will be responsible for ensuring risks to human subjects are minimized, risks are reasonable, subject selection is equitable, the research team has access to adequate resources to conduct the study, the informed consent process (or waiver) meets regulatory and ethical requirements, adequate provision is made to protect human subjects by monitoring the data collected and there are adequate provisions to protect subject privacy per HIPAA regulations and confidentiality of data.

All senior/key personnel and research staff who will be involved in the design and conduct of the study must receive education in human research subject protection from a training program that is approved by a properly constituted independent Ethics Committee or Institutional Review Board. The MPIs will be responsible for ensuring project faculty and staff have the equipment and training required to protect privacy and confidentiality and will monitor and document that these individuals are properly certified. If new senior/key personnel and staff become involved in the research, documentation that they have received the required education will be included in the annual progress reports. The UPENN Office of Regulatory Affairs currently requires HIPAA

training upon designation as research investigator/staff and recertification in human research subjects protection every three years.

The Penn IRB will serve as the IRB of record for any external ethics review boards or IRBs applicable to researchers from other institutions who may have access to human research subjects identified data.

9. Investigator's Risk/Benefit Assessment:

This study presents minimal risk that is balanced by the potential benefits of the research to society.

INFORMED CONSENT:

1. Consent Process:

Aims 1 and 2. Since this is a pragmatic trial focused on improving implementation of higher-value evidence-based practices with minimal risk to patients, we are requesting a waiver of informed consent from clinicians and patients. We have received this in the past for these types of trials. We will identify clinicians at the practice sites and their patients using the EMR.

2. *Waiver of Informed Consent:*

We are requesting a waiver of informed consent and HIPAA authorization from clinicians and patients (see attached request for waiver of HIPAA authorization). A waiver of informed consent is requested for the following reasons. First, it is not feasible to consent every patient and clinician and as mentioned this initiative would occur with or without the study of it. Second, if members of the control (Usual Care) group were consented, they would know they were being studied and this could change their behavior. This could potentially disrupt the design of the study and make interpretation of the findings challenging. Third, clinicians are not being forced to prescribe smoking cessation treatments for their patients. Instead, they are being reminded of evidence-based guidelines and offered an opportunity to review pertinent information and decide to refer to appropriate treatment or not. This is no different than standard of care in which a clinician would review the same information and decide to prescribe. The initiative is simply a reminder for the clinician and makes their standard of care process easier to conduct.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION:

Adequate facilities are available at the ACC. The members of the research team are outlined in HSERA and include appropriate personnel to successfully implement this project. The entire team will be overseen by the PI. All personnel will complete required training before being granted access to any identifying information. This includes training on confidentiality through the Collaborative IRB Training Initiative (CITI) course. All personnel will be trained in the procedures for reporting unintentional breaches in confidentiality to the PI. All personnel will be aware that violations of participants' confidentiality, either unintentional or deliberate, may result in termination of hire. The PI will conduct training with all research personnel regarding data, limits of confidentiality, maintaining confidentiality and proper study procedures.

The following research staff will be directly involved with the implementation and execution of the current study:

Name	Study Role
Frank T. Leone, M.D.	Principal Investigator
Brian Jenssen, M.D.	Principal Investigator
Robert A. Schnoll, Ph.D.	Collaborator
Rinad Beidas, Ph.D.	Collaborator
Justin Bekelman, M.D.	Collaborator
Peter Gabriel, M.D.	Collaborator
Julissa Melo	Informatics/EHR Technician
Anna-Marika Bauer, B.A	Project Manager
Mackenzie Quinn, B.A.	Project Manager
Daniel Blumenthal, B.A.	Clinical Research Coordinator
Sue Ware, B.S.	Database Manager

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