Improving Tobacco Treatment Rates for Cancer Patients Who Smoke

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Study Summary

Title	Improving Tobacco Treatment Rates for Cancer Patients Who Smoke
Short Title	Improving Tobacco Treatment Rates
IRB Number	832404
Methodology	To achieve all of our research objectives, we plan to conduct a two-arm RCT pilot study of a CDS intervention, exposing half of our clinician sample to the TUT Service+VM condition during clinical workflow, and comparing important outcome measures to those observed among the half exposed to the current usual care condition, TUT Service alone.
Study Duration	The study will take place over a period of 2 years.
Study Center(s)	The Penn Presbyterian Medical Center (PPMC) at the University of Pennsylvania will serve as the primary project location, and all recruitment and data collection efforts will be executed by University of Pennsylvania staff members.
Objectives	**Specific Aim 1**: Assess whether including a standing order for prescription and management of varenicline (TUT Service+VM) within the workflow for patients (cancer or non-cancer) identified as current smokers will significantly increase TUT engagement rates compared to current standard of care (TUT Service alone). **Specific Aim 2**: Assess whether clinicians exposed to the TUT Service+VM condition will be more effective at guiding reluctant patients toward TUT engagement than clinicians exposed to the TUT Service alone condition. **Specific Aim 3**: Assess implementation preferences and barriers influencing effectiveness of usual care tobacco use treatment (TUT Service) + varenicline management (VM) applied within the cancer center.
Number of Subjects	Recruitment will include projected subject recruitment totals of 52 PPMC clinicians.

Main Inclusion and Exclusion Criteria	**Subject Inclusion Criteria:** • Provides care for inpatients with a cancer diagnosis at PPMC as a hospitalist or attending in the Department of Medicine • Prescribing authority in Pennsylvania (i.e. physician, nurse practitioner, physician assistant); • Has cared for at least one patient with tobacco use disorder in the 30 days prior to recruitment; • English speaking
Intervention	Our research objective is to identify a simple, pragmatic, innovative way of enhancing TUT rates within medical care, including oncology. To investigate this possibility, we propose methods that will allow us to: 1) evaluate the impact of standing orders to initiate a varenicline management protocol within inpatient cancer and non-cancer treatment workflow and 2) assess the potential for an EHR-based intervention to affect patient TUT behaviors.
Statistical Methodology	For Aims 1 and 2, rate comparisons between the two groups will be performed using Chi-square. For Aim 3, average scores will be calculated for ratings of barriers and facilitators to effectiveness of implementing VM,
Data and Safety Monitoring Plan	The study will be monitored by the PIs and co-investigators, and regulatory committees at the University of Pennsylvania (i.e., IRBs, OHR). During the course of the study, safety and data quality monitoring will be performed on an ongoing basis by the Principal Investigator and the study staff.

1 Introduction

To reduce all-cause and cancer-specific mortality, the 2014 Surgeon General's Report emphasized the importance of effective tobacco use treatment (TUT) in within medical care, including cancer care.(1) Unfortunately, up to 50% of cancer patients who smoke prior to their diagnosis continue to do so after diagnosis and treatment.(2) This observation has lead the National Comprehensive Cancer Network,(3) the American Society of Clinical Oncology,(4) and the American Association for Cancer Research(5) to call for implementation strategies integrating TUT directly within oncology care. At this time, many cancer centers and oncology practices, and general inpatient medical facilities, fall short of providing consistent, high-quality TUT; only half of cancer centers report that they identify tobacco use among patients,(6) and very few use systematic mechanisms to encourage TUT services.(5)

In response, the National Cancer Institute (NCI) funded the Cancer Center Cessation Initiative (C3I) in 2017 with support from the NCI Cancer Moonshot Program.(7) C3I's aim is to help build and sustain TUT infrastructure across the nation's cancer centers, ensuring that cancer patients are systematically screened for tobacco use and provided with evidence-based smoking cessation treatment.(8) Abramson Cancer Center's work implementing the C3I tobacco use treatment service (TUT Service) has

significantly improved rates of TUT within oncology practice, however we have identified a number of important social-motivational obstacles to reaching our target of universal TUT. For instance, we know that simple changes to treatment choice architecture in the electronic health record (EHR), i.e. utilizing an "opt-out" rather than "opt-in" structure, increases TUT Service engagement in a manner similar to other contexts of cancer care.(9) Unfortunately, there remains unacceptable variation in clinician engagement rates. One significant reason for this variation is the individual clinician's perceptions of treatment effectiveness.(10–12) A strategy used elsewhere involved utilizing opt-out orders aimed at maximizing the use of varenicline, i.e. "Varenicline Management" (VM). VM resulted in increased clinician utilization and patient cessation within a relatively controlled environment of hospital-based cardiac and pulmonary care.(13,14) However, it is unknown whether this type of intervention is generalizable to the complex, challenging environment of inpatient oncology.

Our research objective is to identify a simple, pragmatic, innovative way of enhancing TUT rates within inpatient medical care and, specifically, for oncology inpatients. To investigate this possibility, we propose methods that will allow us to: 1) evaluate the impact of standing orders to initiate a varenicline management protocol within inpatient medical treatment workflow (that will include cancer and non-cancer patients) and 2) assess the potential for an EHR-based intervention to affect patient TUT behaviors.

1.1 Study Significance and Rationale

Insights from prior work: Our group has been engaged in efforts to understand the behavioral economic landscape informing clinician choice for several years. In a discrete choice analysis of alternatives determining physicians' preferences for generic "smoking cessation strategies," effectiveness of the intervention was a statistically significant determinant of preference, with a relative utility 100-fold greater than either reimbursement rate or time saving capacity. This observation led us to examine the role of several cognitive biases in influencing physicians' perceptions of success probabilities under conditions of uncertainty.(11) Educational efforts that minimize availability bias, omission bias, impact bias and focusing effect bias more successfully change physician TUT behaviors than interventions aimed solely at increasing knowledge.(33) Our group also identified implicit associations between smoking status and a culpability theme, influencing both the emotional characteristics of physician-smoker interactions and willingness to invest effort in TUT.(34) It is clear that complex and overlapping social motivators play a significant, perhaps unrecognized, role in physician decision-making around TUT.

Finding solutions: Addressing a variety of complex motivations, within a diverse group of clinicians from multiple disciplines, with widely divergent perceptions about and experience with TUT, will require an approach that moves beyond traditional behavior change communications (BCC), and integrates several different theory-based behavioral economic (BE) interventions within a cohesive theme (Fig 1).(35) Our project represents an innovative approach to incorporating several BE insights into a simple, practical, system change that has the potential to meet a variety of needs. At baseline, our CDS facilitates identification of smoking status, and relies on harnessing social norms to encourage physicians to opt-in. Our varenicline management (VM) intervention (described in full below) adds several BE dimensions to the CDS, namely: 1) removal of obstacles to decision-making

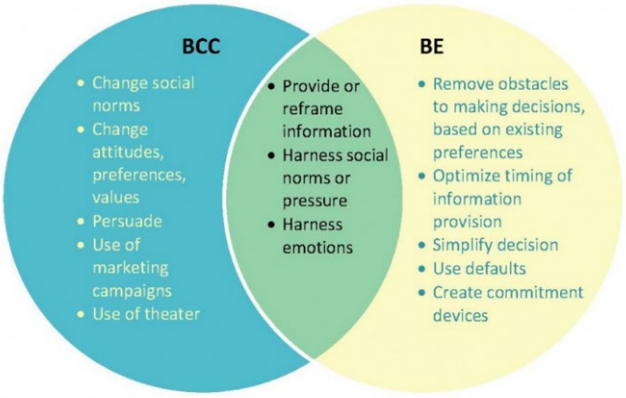

Figure 1: Continuum of interventions ranging from Behavior Change Communications to Behavioral Economic influences on choice.

at the moment of treatment planning and order entry, 2) optimization of timing of information-giving by moving medication management to outside the cancer care visit, 3) simplifying treatment decisions by focusing the palette of pharmacotherapies to the one generally recognized as most effective (36), 4) using an opt-out choice architecture to take advantage of defaults, 5) maximizing clinician perceptions of effectiveness by presenting relative efficacy data directly within the order field, and 6) acting as a very strong commitment device, encouraging both clinicians and patients to engage in important follow-up activities.

Why varenicline: The initial 2006 reports of varenicline's impact on tobacco dependence suggested superior efficacy to other available pharmacotherapies, including nicotine replacement and bupropion.(36,37) Since then, varenicline has been generally well accepted as first-line therapy in a general population of smokers, with an abstinence odds ratio (OR) of ~2 when compared to other pharmacotherapies.(38) Cancer patients are *not* more likely to spontaneously quit because of their illness (39), however studies have confirmed varenicline's similar efficacy in cancer patients who continue to smoke.(40) Initial concerns over the possible neuropsychiatric side-effects of varenicline appear to have been overblown(41), with the most recent and comprehensive data suggesting efficacy, safety, and tolerability, even in patients with pre-existing depression and psychiatric disease.(42) Perhaps most encouraging is the observation that varenicline is effective in promoting cessation even in patients unwilling to make a quit attempt at the time of treatment initiation, making it the ideal candidate for a CDS intervention designed to produce minimal interruption to oncology treatment workflow.(43–45)

2 Study Objectives

The multi-disciplinary team assembled for this study implemented the ACC TUTS program. Drs. Schnoll and Leone oversee this program. This is a pragmatic study. The specific aims are described below.

2.1 Primary Objectives

The objective of this study is to examine a novel approach to improving the quality of care inpatients receive if they use tobacco (oncology and general inpatients).

Specific Aim 1: *Assess whether including a standing order for prescription and management of varenicline (TUT Service+VM) within the inpatient clinical workflow for cancer and non-cancer patients identified as current smokers will significantly increase TUT engagement rates compared to current standard of care (TUT Service alone).* Hypothesis: Observed treatment engagement rates will be higher among clinicians exposed to TUT Service+VM than observed in clinicians exposed to TUT Service alone.

Specific Aim 2: *Assess whether clinicians exposed to the TUT Service+VM condition will be more effective at guiding reluctant patients toward TUT engagement than clinicians exposed to the TUT Service alone condition.* Hypothesis: Rates of important TUT behaviors (e.g. treatment initiation, quit attempts, and others) observed among smoking patients of clinicians exposed to TUT Service+VM will be higher than those than observed among smoking patients of clinicians exposed to TUT Service alone.

Specific Aim 3: *Assess implementation preferences and barriers influencing effectiveness of usual care tobacco use treatment (TUT Service) + varenicline management (VM) applied within the cancer center.* Hypothesis: Oncology specialists exposed to the TUT Service + VM condition will identify key facilitators and barriers to the implementation of the TUT Service + VM condition that can help guide subsequent dissemination efforts.

The goal of this study is to determine if the default for a varenicline order increases clinician referral to TUTS and/or the treatment of tobacco use. At this point, many clinicians are turning the referral order off and patients are not receiving treatment for tobacco use. A default to prescribe treatment may help override barriers to both. While we are focused on cancer inpatients, we will assess the impact of the varenicline management intervention on cancer and non-cancer patients.

Insights gained from this project form the basis of subsequent clinical trials assessing efficacy of novel implementation approaches improving uptake of evidence-based tobacco use treatment within the inpatient clinical setting. This study is significant because the model for promoting physician behavior change is simple and pragmatic yet has the potential to significantly impact patient survival and morbidity. The study builds on previous observations made through NCI and C.U.R.E. investments, expanding our understanding of novel pharmacologic approaches to tobacco cessation.

3 Study Population and Duration of Participation

The study will be conducted within PPMC in the University of Pennsylvania Health System (UPHS). Participants will be hospitalist and attendings in the Department of Medicine who provide care for inpatients with a cancer diagnosis at PPMC. This study will recruit individuals age 18 or older only. Children under age 18 will not be eligible for this trial.

We plan to derive a sample of 52 clinicians from the available pool of several hundred eligible PPMC clinicians.

No data are to be collected from the patients aside from routinely collected patient-level data regarding tobacco treatment use once patients are referred to Dr. Leone's tobacco treatment program; patient data are available in the EHR. If clinicians place the referral order (which is already in EPIC) to Dr. Leone's smoking cessation service, we collect standard information concerning smoking behavior that is standard clinical information, not research data (e.g., use of smoking cessation treatments, quit attempts). No patient data will be collected outside of what is available in the EHR (for clinicians in the study) or what is collected clinically when patients contact the cessation program from the clinician's referral. All patients receiving care from eligible clinicians will be assessed in this study as described above, those with or without cancer, so that we can test the impact of the intervention for cancer inpatients as well as for those inpatients without a cancer history.

3.1 Duration of Study Participation

The study will take place over a period of 2 years. Therefore for 18 months, data will be collected and analyzed from the clinicians' clinical practice on a quarterly basis.

3.2 Total Number of Subjects and Sites

A total of 52 clinicians will be recruited to participate in the study from PPMC

3.3 Inclusion Criteria

Clinic clinician participants must meet the following criteria for enrollment:
1) Provides care for inpatients with a cancer diagnosis at PPMC as a hospitalist or attending in the Department of Medicine,
2) Prescribing authority in Pennsylvania (i.e. physician, nurse practitioner, physician assistant),
4) Has cared for at least one patient with tobacco use disorder in the 30 days prior to recruitment,
5) English speaking

3.4 Exclusion Criteria

Exclusions include:
1) Unwillingness to prescribe varenicline, or
2) Unwillingness to assign varenicline management to TUT Service providers.

There will be no exclusion based on gender or race/ethnicity, consistent with our demonstrated ability to recruit representative samples in terms of demographic characteristics.

3.5 Subject Recruitment

ACC provides the highest quality medical care across the cancer care continuum to ~10,000 patients/year, reducing the cancer burden within an ethnically diverse catchment area consisting of 15 counties within the Greater Delaware Valley. We have extensive experience implementing tobacco research within clinics and working with clinicians on smoking cessation research (Schnoll et al., 2003; Schnoll et al., 2010). In a past study, we were able to recruit >200 primary care clinicians for training in treating nicotine dependence over 9 months (Leone et al., 2015), and in 14 months of recruitment in our ongoing organizational intervention trial (R01 CA202699), we have recruited 8 clinics, 295 patients and 120 clinicians. Further, Dr. Leone, my close collaborator, has evaluated Clinical Decision Support Tools for promoting the treatment of tobacco dependence in Penn primary care.

Study leadership will first engage the ACC and its clinicians about the study. Dr. Schnoll is the Associate Director for Population Science at the ACC and regular (weekly) interactions with Larry Shulman, Chief of the Cancer Service Line. Dr. Shulman, along with Drs. Metz and Shuchter (Radiation and Medical Oncology chairs) and Drs. Schnoll and Leone (and Dr. Peter Gabriel), developed the Tobacco Use Treatment Service together. The proposed study, which simply adds a new default for an FDA-approved treatment for smoking, builds off of this collaboration. If the grant is supported, this team will work together to implement the proposed study.

Recruitment of clinicians will proceed via service-line leadership. Leaders of the Department of Medicine's hospital-based service lines (Teaching Medicine and Hospitalist services) will be briefed on the purpose and procedures for the study. Upon agreeing, a detailed email will be sent to individual admitting clinicians within each service line in order to inform them of the intent to alter the alert. The email will conclude with contact information for study personnel, in order to report questions, concerns or problems with the proposed workflow. Recruitment to participation is passive, absent notification to the contrary.

The same clinician sample will be contacted via email to participate in the survey supporting Specific Aim 3. This recruitment email will detail the goals of the survey, outline potential compensation, provide ways for clinicians to contact the study team with questions, and will note the voluntary and confidential nature of the study.

3.6 Vulnerable Populations

Population protected under HHS regulations 45CFR46 Subparts B, C, & D Study Procedures: Children, neonates, and prisoners are not included in this research study. Women who are pregnant at the time of baseline assessments will be eligible for the study.

Populations vulnerable to undo influence or coercion: Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons are not included in the current study. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate. Status of participation in the study will be independent of the subject's work or school activities.

4 Investigational Plan

4.1 General Design

To achieve all of our research objectives, we plan to conduct a two-arm RCT pilot study of a CDS intervention, exposing half of our clinician sample to the TUT Service+VM condition during clinical workflow and comparing important outcome measures to those observed among the half exposed to the current usual care condition, TUT Service alone. Following the conclusion of the pilot study, clinicians will be surveyed about implementation preferences and barriers influencing effectiveness of the intervention.

4.2 Study Measures

Our current usual care CDS "fires" a Best Practice Alert (BPA) for each new inpatient within the Medical Assistant (MA) check-in and vital sign workflow. The BPA requires that MAs assess tobacco use status within the past 30 days and satisfy the alert with one of three possible, mutually exclusive answers.

Intervention ordering rate is defined as the number of patients for whom any inpatient tobacco use treatment order (for medication, education, and/or TUTS counseling) was signed divided by the total number of patients in each arm for whom an order was pended and the alert fired. MAs activate "Order" tab for all patients identified as current smokers (within 30 days), resulting in placement of pended order for consult to TUT Service referral within clinical workflow.

Inpatient medication ordering rate is defined as the number of patients for whom a tobacco use treatment medication was ordered in the inpatient setting divided by the total number of patients in each arm for whom an order was pended and the alert fired.

Outpatient/discharge medication ordering rate is defined as the number of patients for whom a tobacco use treatment medication was ordered upon patient discharge from the hospital divided by the total number of patients in each arm for whom an order was pended and the alert fired.

TUTS referral rate is defined as the number of patients for whom a referral to Penn Medicine's Smoking Cessation Program was placed in the inpatient setting divided by the total number of patients in each arm for whom an order was pended and the alert fired.

These measures will be collected only from patients referred to Dr. Leone's program for treatment:

Quit Line rate, defined as the total number of patients who present for quit line counseling (i.e. telephone or electronic), divided by the total number of patients referred to the Smoking Cessation Program

Medication recommendation rate, defined as the total number of patients who are recommended to receive a tobacco use treatment medication by the TUT Service staff in quit line counseling divided by the total number of patients who present for quit line counseling

Follow-up recommendation rate, defined as the total number of patients who are recommended to receive a tobacco use treatment medication or a follow-up appointment by the TUT Service staff in quit line counseling divided by the total number of patients who present for quit line counseling

Proposed survey measures, including ease and appropriateness, are noted in the attached survey form and will be submitted to the IRB for review prior to survey launch.

5 Study Procedures

5.1 Usual Care (control condition)

The TUT Service utilizes the Ask, Advise, and Connect referral framework.(28) This approach utilizes CDS logic embedded within the new patient intake routines. Standardized mandatory assessment of smoking status for all oncology patients automatically integrating cancer-relevant cessation advice in the written After Visit Summary (AVS), and sends an electronic referral to Certified Tobacco Treatment Specialists (CTTS) trained in the unique counseling requirements of patients.(51) Counselors assess the patient's educational, emotional, interpersonal, and skill-based needs, and develop a treatment recommendation based on the patient's priorities. The goal is to direct the patient to ongoing clinical services, either in a face-to-face setting or via telephone/digital quit line support.

5.2 Novel BE intervention

Our VM intervention builds upon the established TUT Service process. In addition to connecting the patient to TUT Service via electronic referral, it activates a medication management protocol that: 1) actively confirms no evidence of renal failure or pregnancy with the provider, 2) automates a referral to prescribing providers within the TUT Service team, prompting a call-back to patient within 24 hours, 3) provides written AVS instructions to contact TUT Service for initiation instructions and clinic appointment, and 4) pends a varenicline prescription to the medication list, ready for reconciliation by TUT Service prescribing clinicians. The protocol formalizes standard management principles for varenicline, including follow-up evaluation, pre-quit period duration, and side effect amelioration.(52)

5.3 Varenicline Management

The Research intervention in this protocol is best described as a two-step procedure for transferring responsibility for tobacco dependence medication management and follow-up to a recognized consulting clinical service. The steps: 1) Upon executing the order for "Varenicline Management Protocol" in the patient's electronic record, the subject clinician automatically sends an electronic alert the Tobacco Use Treatment team, indicating their desire to begin varenicline pharmacotherapy as part of the patient's cancer care; 2) A prescribing provider within the tobacco use treatment team initiates standard clinical care of the patient within 24 hours of the order, focused on initiating pharmacotherapy of tobacco dependence using current evidence-based guidelines of care.

As background, recognize that "standard clinical care of the patient" in this context includes:

i) contacting the patient to ascertain suitability for varenicline therapy, including history of prior use, insurance coverage, etc.

ii) ascertain the presence of any potential complications of varenicline use (i.e. current pregnancy, uncontrolled seizure disorder) or necessary dose adjustments (i.e. reduced creatinine clearance)

iii) educate patient regarding proper use and anticipated effects of varenicline, including proper dosing, schedule, possible side effects, and available alternatives.

iv) providing patient with written information regarding the medication

v) arrange for an outpatient visit in clinic to follow-up, provide dependence counseling, and make medication adjustments as needed.

5.4 Inclusion of Non-cancer Patients

After testing the logic of the usual care intervention and the Novel BE intervention, it was determined that these two groups were being treated differently. In the usual care intervention, clinicians would receive the standard TUT Service BPA for all patients, regardless of cancer status. However, in the Novel BE intervention, the clinicians would receive the TUTS + VM BPA for their patients with a cancer history but would also be exposed to the standard TUT Service BPA for their patients without a cancer history. To ensure that these two groups are experiencing the same treatment, we are altering the study logic so that the clinicians randomized to the study Novel BE intervention will be exposed to the TUTS + VM BPA regardless of a patient's cancer status. This will also allow us to test the effect of the intervention on all inpatients, on non-cancer in-patients, and on just cancer inpatients. This change simplifies the system and expands our ability to test the impact of the intervention on differing in-patient populations.

5.5 Data Collection

All clinicians and sites use EpicCare (Epic Systems Corporation, Verona, WI) to deliver care. Penn Medicine Information Systems (IS) - Colin Wollack, Penn EPIC Research Team - oversees successful integration of TUT Service CDS into ACC workflow. Ms. Chen generates quarterly reports and delivers them electronically to the TUT Service managers (Ms. Evers-CaseyFischer, and Nicoloso). Aim 1 & 2 data is of high quality; each report is assessed for quality and accuracy through review of the primary medical record in a random subset of instances. Aim 2 utilizes self-reported measures of effect, derived from in-person clinical (CTTS) contact, providing multiple opportunities to confirm the accuracy of self-reported status. Our experience to date suggests that these measures are highly reliable global metrics. To protect subject privacy, clinician decision-making and patient health record security is stronger than with most other web-based utilities. Numerous layers of data security ensure confidentiality. Data Transfer is exclusively via SSL encryption, protecting data transfer between staff. This is the same technology that is used to protect consumer information (e.g., credit cards) from interception in transit over the Internet. All research data is stored in a secure Oracle database housed behind secure health system firewall.

5.6 Administration of Surveys and/or Process

Clinicians will be invited to complete a survey in the fall of 2023. We anticipate that this survey will take no more than 10 minutes to complete. The survey will measure clinician characteristics, opinions and experiences using the best practice alerts from the study, and related cognitive biases. We will keep the number of items as low as possible to reduce clinician fatigue and increase response rates. Please see the attached survey form for more detail.

Survey data will be collected through REDCap (a secure, web-based application for collecting and managing survey data that can be completed via computer or mobile device). Clinicians from the initial pilot (Aims 1-2) will be sent a link to the REDCap form via email. If a clinician clicks the link to learn more about participating, they will be routed to a webpage within REDCap that outlines all required consent elements. If they decide to participate, they will click a button which will route them to the first page of the survey. Clicking this button indicates their agreement to participate in this aim of the study. See the **Informed Consent** section for more details regarding this process.

5.7 Subject Withdrawal

Participants may choose to withdraw from the study at any time. They do this by providing verbal or written communication to this effect. Withdrawal from the study will not impact employment status within the cancer center. The Principal Investigator may withdraw subjects who violate the study plan, to protect the subject for reasons related to safety or for administrative reasons. Whether or not each subject completes the study will be tracked.

5.8 Timeline

Over 2 years, our multi-disciplinary team will plan, implement, and evaluate, the project. **Aims 1-2** of the project will be accomplished by organizing tasks into four main areas. Planning, which is already fully underway, involves assembly and training of the multi-disciplinary team, refinement of key project elements, recruiting clinician participants, and modification of the CDS logic. Given our ongoing planning, we expect needing only 3 months before moving into the next phase. Implementation involves program initiation, roll-out of the TUT Service+VM CDS protocol, and preparation of evaluation tools. We expect to have the CDS fully operational by month 7. Evaluation will start within one calendar quarter of implementation, and will run for the duration of the project.

Months/Task	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	thru	24
Plan																	
Implement																	
Evaluate																	
Sustain																	

6 Statistical Plan

All data will be maintained on password-protected computers within a DMS that uses ORACLE and MS ACCESS to permit web-based real-time data entry, storage, and QA.

6.1 Sample Size and Power Determination

Engagement rates are our primary measure of effect. Given that our initial educational intervention was able to change absolute engagement rates by approximately 20%, we assume that a CDS intervention would need to accomplish an equivalent amount of change to be clinically relevant. There are over 1000 BPA activations annually, resulting in approximately 600 TUT Service referrals per year (Engagement rate ~ 60%). To detect improvement in Engagement rate to 80%, with 80% power and a significance level of p=0.05, we need to enroll 24 clinicians to each arm. Retention: Because of project nature, we assume drop-out will be minimal (<10%) after enrollment; 26 subjects per arm ensures power.

6.2 Statistical Methods

For Aims 1 and 2, rate comparisons between the two groups will be performed using Chi-square. We will examine the impact of the intervention on tobacco treatment rates across cancer inpatients, non-cancer in-patients, and all in-patients.

7 Safety and Adverse Events

7.1 Data Safety Monitoring Plan (DSMP)

Because of the nature of the project, and the minimal risk to participant privacy, we do not plan to constitute a formal Data Safety Monitoring Board. However, 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.

7.2 Internal Monitoring and Auditing

The study will be monitored by the PI and regulatory committees at Penn (i.e., IRBs, OHR). The following monitoring activities will be conducted according to standard operating procedures. These activities will be performed in association with database auditing and facilities monitoring by the Penn OHR and/or study personnel.

Initial Assessment Monitoring: Penn OHR will conduct a manual review of source documents and Case Report Forms (CRFs) for a random subset of participants enrolled in the study. This inspection is the visual comparison of source documents to CRFs in a quantitative assessment of accuracy based on the number of data fields. A brief, internal report will be generated to describe findings. If the data are less than acceptable, additional cases are requested, with appropriate counseling/training for staff.

Protocol Monitoring: Protocol monitoring includes a survey of those activities that are associated with protocol adherence such as study visit deviation and violation of inclusion/exclusion criteria. A specific protocol monitoring plan will be used. All accrued cases will be subjected to protocol monitoring throughout the duration of the trial.

Database Auditing: Ms. Ware and the RA will review data entered into the database versus that recorded on the CRFs. All accrued cases will be subjected to database auditing throughout the trial. Depending on the data management findings, re-training will be provided, should problems such as increased errors be detected.

Data Auditing: Ms. Ware and the RA will review safety data recorded on the CRF versus that contained on the actual source document (patient chart, EHR). All accrued cases will be subjected to auditing throughout the duration of the trial. A Regulatory Binder Review by OHR will include the following essential documents: IRB Protocol, Amendment Approvals, IRB Closure Letter, List of Authorized Signatures, Laboratory Certifications, Protocol and Amendment Signature Pages, Financial Disclosure Questionnaires, and Monitoring Log. Additional monitoring by OHR may include: source documentation verification; adverse event documentation; and facility assessment.

Data Security: Using network firewall technologies, the database will prevent the three major sources of data security problems: unauthorized internal access to data, external access to data, and malicious intent to destroy data and systems. Controlled user access will ensure that only appropriate and authorized personnel are able to view, access, and modify trial data. All modifications to data will document user access and data associated with the modification, as well as values prior to modification.

IRB Monitoring: The protocol will be reviewed by the Penn IRB and will only be implemented after successful approval from the IRB. Annual reporting and auditing will be conducted by the IRB. All procedures will be approved by the IRB. A protocol-specific Data Safety Monitoring Board will not be used for this study since it is not a clinical trial. The Penn IRB will ensure participant safety and data integrity.

Evidence of Training in Human Subject Research: All personnel working on this project will be required to review the protocol, complete training in the protection of human subjects (developed and implemented by the Penn IRB), and undergo training.

7.3 Reporting of Adverse Events and Unanticipated Problems

The Principal Investigator will promptly notify the Penn IRB of all on-site unanticipated, Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10 working days.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

The Data Management System has set up several safeguards to prevent unauthorized access to study data. An automatically generated index number is assigned to a clinician subject's study identification number (unique for clinicians). A linked subject identification table is created for the storing of subject name, address and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information tables are maintained in a separate database. Using this method, no identifying subject information is directly linked to medical information or other study data. For our multi-site trials, we have long-established protocols to guard against improper use of hard copies of data (e.g., locked files, numeric coding procedures). The present research team has not experienced the unauthorized use of study data. A web-based data collection procedure will minimize the possibility of loss of privacy or confidentiality.

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.

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.

The following personal health information will be collected as part of this study:

1. Name
2. Address
3. Date of Birth
4. Phone number(s)
5. Electronic mail address
6. Cancer History
7. Medical Record Number
8. Tobacco Use History

For patient data collected from electronic medical records, as soon as patient data is received by the study staff, all identifiers will be destroyed and replaced with an identification number unique for patients. Using this method, no identifying subject information is directly linked to medical information or other study data.

8.2 Sources of Research Material

All data collected for this study will be used solely for the purpose of the present study and will be treated with full confidentiality. The only information collected to be used for research purposes will be from the qualitative interview concerning attitudes about the implementation of the TUTS program.

The integrity and security of the data will be maintained as described below

8.3 Computers and Databases

Personnel at Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) have personal computers linked to a common computer server. The CIRNA maintains a LAN to allow for remote access to common software and computer files. This LAN maintains all necessary communications, word-processing, and data management systems (DMS). Data (for all studies, including the one proposed here) are maintained on password-protected computers and are maintained on a DMS overseen by CIRNA staff. The DMS uses ORACLE and MS ACCESS to permit real-time data entry, storage, and QA by web-based access and scannable forms, which increases standardization. We have >15 years of experience with this DMS for similar trials. The DMS constructs semantic constraints on fields, and is used for data entry, storage, retrieval, and security. The DMS mimics the appearance of CRFs completed at visits. Each visit date is “mile-stoned” (e.g., completed, scheduled, missed). During data entry, validation occurs via built-in mechanisms (e.g., Range Checks - data range restricted). Daily backups occur to protect against corruption or deletion. Protection of privacy is ensured by: minimizing use of identifying information, use of ID numbers vs. names, keeping all data in locked files, and restricting access to the dataset linking names with ID numbers. Currently, this DMS is used for several multi-site smoking cessation clinical trials (e.g., R01 DA025078; R01 CA165001). This web-based DMS allows for the simultaneous running of the trial at multiple sites using standardized systems. The same system will be used for the proposed study. All information from the study (i.e., transcripts of interviews) and the results of the qualitative analyses will be stored within this DMS.

9 Ethical Considerations

9.1 Risks and Protections

Potential Risks.
Risk to subjects is considered minimal. Risks are limited to subject privacy/confidentiality.

Threats to Privacy/Confidentiality: Since information provided by participants will be recorded and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the Data Management System has set up several safeguards to prevent unauthorized access to study data. An automatically generated index number is assigned to a subject's study identification number (unique for clinicians). A linked subject identification table is created for the storing of subject name, address and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information tables are maintained in a separate database. Using this method, no identifying subject information is directly linked to medical information or other study data. For our trials, we have long-established protocols to guard against improper use of hard copies of data (e.g., locked files, numeric coding procedures). The present research team has not experienced the unauthorized use of study data. A server-based data collection procedure will minimize the possibility of loss of privacy or confidentiality.

Protection Against Risks. The following methods will be employed to minimize participant risk.

To protect subject privacy, clinician decision-making and patient health record security is stronger than with most other web-based utilities. Numerous layers of data security ensure confidentiality. Data Transfer is exclusively via SSL encryption, protecting data transfer between staff. This is the same technology that is used to protect consumer information (e.g., credit cards) from interception in transit over the Internet. All research data is stored in a secure Oracle database housed behind secure health system firewall.

In accordance with NIH and IRB guidelines, this protocol will employ the following mechanisms for adverse event reporting: 1) alert the IRB of any and all reports of serious adverse events; 2) informing all members of the study team of any and all reports of serious adverse events; and 3) notification to NIH of any actions taken by the IRB with regard to data safety monitoring.

9.2 Benefits

By addressing obstacles to tobacco treatment engagement, this project has the potential to reduce treatment burdens for clinicians, improve clinicians skill with tobacco treatment techniques and pharmacotherapies, improve cancer treatment outcomes, and reduce morbidity from treatment related complications.

9.3 Compensation

Aim 3 surveys: Participating clinicians will have the opportunity to receive a $25 Amazon gift card once they complete the survey.

9.4 Risk Benefit Assessment

Evolving National Cancer Institute priorities have made rapid adoption of evidence-based TUT an essential component of comprehensive care. To date, little is known of the relative impact of BE strategies to systematically influence clinician decision-making abut tobacco. The proposed study will test the notion that a simple, practical, electronic CDS intervention can significantly influence the clinical behaviors of both clinician and patient. As a result of this project, novel approaches to influencing clinical behaviors will be identified, forming the basis of a subsequent large-scale clinical trial assessing effectiveness under real-world conditions. This study is significant because the VM model for promoting clinician behavior change may also be applicable to other, non-cancer disorders, such as opioid dependence. If effective, the VM intervention would represent an inexpensive, straightforward way to reduce cancer morbidity and

mortality, and reduce the cost of cancer care incurred by both patients and the Commonwealth. The potential benefits of this study outweigh the potential risks.

10 Informed Consent

10.1 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.

Aim 3. Participants will provide informed consent before completing survey measures. Because surveys will be completed remotely via REDCap, e-consent will be obtained as we have done previously (IRB 844846). When potential participants click the link to participate, they will be directed to a page within REDCap that outlines the required elements of informed consent. If they agree to participate, participants will indicate consent by clicking the “next” button which will take them to the electronic survey. If they do not want to participate, they will simply close the window.

All potential participants will be informed that participation is voluntary and they will be provided with the information that they need to make an informed choice. We will provide contact information to all potential survey respondents in case they have any questions before, during, or after completing the survey.

10.2 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.

For Aim 3, we are requesting a waiver of ***written*** documentation of consent from the Penn IRB. Surveys will be completed via REDCap. During these instances, we will not have an opportunity to collect a signed copy of the consent form. This research activity presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

11 Resources Necessary for Human Research Protection

11.1 Qualifications of Investigators

Drs. Schnoll and Leone have been centrally involved in understanding and treating nicotine dependence in cancer patients for 20 years. They have documented factors associated with continued smoking (56,57) and barriers to treatment engagement (58, 59). They have developed and evaluated behavioral counseling interventions specific to cancer patient barriers, including low motivation, depression, and fatalism (61), evaluated pharmacologic cessation interventions (40,62,63), and documented the

feasibility of extending tobacco cessation treatment to patient family members who smoke.(23) This experience, along with Dr. Schnoll's leadership position at the cancer center and Dr. Leone's expertise with system-based tobacco treatment interventions(10,31,33) will help ensure the success of the project. The following research staff will be directly involved with the implementation and execution of the current study:

Name	Study Role
Robert A. Schnoll, Ph.D.	Principal Investigator
Frank T. Leone, M.D.	Co-Principal Investigator
Sarah Evers-Casey, M.P.H, CTTS-M	Collaborator
Tierney Fisher, D.N.P., CRNP	Collaborator
Jody Nicoloso, CTTS-M	Collaborator
Colin Wollack, M.S.	Informatics/EHR Technician
Daniel Blumenthal, B.A.	Project Manager
Sue Ware, B.S.	Database Manager
Joseph Smith, B.S	Database Assistant
Paul Wileyto, PhD	Biostatistician
Nathaniel Stevens, B.A.	Research Assistant

12 Study Finances

12.1 Funding Source

This study is financed through a grant from the Commonwealth of PA.

12.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13 Publication Plan

We will follow standard methods for publishing the results of this study and in accordance with any publication policies of the University, Department, Division or Research Center.

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