Optimizing Tobacco Dependence Treatment in the Emergency Department

IRB Protocol and Statistical Analysis Plan

PI: Bernstein, Steven L.

NCT #: NCT02896400

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YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Optimizing Tobacco Dependence Treatment in the Emergency Department			
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Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☒ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

APPROVED BY THE YALE UNIVERSITY IRB 2/28/2020

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI
o Yes o X No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?
o Yes o X No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

- ☐ Magnetic Resonance Research Center (MR-TAC)
- ☐ Yale Cancer Center/Clinical Trials Office (CTO)
- ☐ Yale Cancer Center/Smilow
- ☒ Yale-New Haven Hospital
- ☐ Cancer Data Repository/Tumor Registry
- ☐ Specify Other Yale Location:
- ☐ Yale University PET Center
- ☐ YCCI/Church Street Research Unit (CSRU)
- ☐ YCCI/Hospital Research Unit (HRU)
- ☐ YCCI/Keck Laboratories
- ☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

- ☐ APT Foundation, Inc.
- ☐ Connecticut Mental Health Center
- ☐ Clinical Neuroscience Research Unit (CNRU)
- ☐ Other Locations, Specify:
- ☐ Haskins Laboratories
- ☐ John B. Pierce Laboratory, Inc.
- ☐ Veterans Affairs Hospital, West Haven
- ☐ International Research Site

(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☒ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Yale University RSC (YU-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ *Nursing Research Committee Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   7/1/16-6/30/20

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☒ **N/A**
   ☐ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☒ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒ NCT02896400

Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
Yes ☐ No☒

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.*

Yes ☒ No☐

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No __X_ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level

practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Bernstein, SL.	Optimizing Tobacco Dependence Treatment in the Emergency Department	NIH – National Cancer Institute	☒ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☒ Grant-M# 1R01 CA201873-01A1 ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health**

Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.

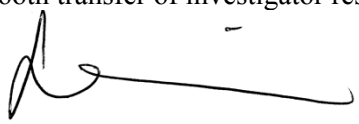
SEE IRES-IRB

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.



PI Name (PRINT) and Signature

3/3/16
Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)

X No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)

X No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

Lori Post _____ 3/8/16
Chair Name (PRINT) and Signature Date

Emergency Medicine
Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____
YNHH HSPA Name (PRINT) and Signature Date

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

The **specific aims** of this proposed study are:

Aim 1. To conduct a fully powered factorial randomized trial of **1056** adult smokers to test the efficacy of 4 key components of ED-initiated tobacco treatment: MI, NRT, QL referral, and SMS texting.

Aim 2. To identify the most efficacious components of our intervention, within fixed constraints of cost effectiveness and feasibility/acceptability to providers and subjects.

Aim 3. To lay the groundwork for a future randomized trial testing the previously identified components, delivered as a package, against a control arm in a new cohort of adult ED smokers.

Our associated **hypotheses** are:

1. At 3 months, at least 1 intervention component will yield a biochemically verified tobacco abstinence rate at least 5% greater than in the control condition.
2. At 3 months, at least 1 intervention will be cost-effective, using a societal perspective.
3. At 3 months, at least 1 intervention will be acceptable and feasible to providers and subjects.

In Year 4, we will propose a randomized clinical trial to test, as a package, the components identified as both clinically effective and cost-effective.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Fifty years after the landmark 1964 Surgeon General's report, smoking remains the leading cause of preventable death in the United States, with about 480,000 deaths per year.[1] In 2012, $289 billion in direct and indirect costs were associated with tobacco use. In 2012, 18.1% of Americans smoked,[2] still far short of the Healthy People 2020 goal of 12% prevalence.[3] Certainly, much progress has been made. However, after half a century of research, regulation, policy advances, drug development, public service campaigns, and litigation, it is apparent that smoking has increasingly become an addiction that disproportionately affects the medically disadvantaged: those with low income or low education, the mentally ill, and individuals with other substance use disorders. These are among the groups identified in a 2006 NIH State-of-the-Science conference as those most in need of advances in treatment and treatment engagement.[4]

These groups of smokers are commonly treated in hospital emergency departments (EDs). EDs are a frequent site of care for all Americans, with approximately 136 million visits across 4000 EDs in 2011.[5] ED patients are disproportionately of low socioeconomic status, more likely to smoke compared with the general population, [6,7] and more likely to have limited or irregular access to primary care. ED smokers often present with illnesses caused or exacerbated by tobacco use, or have injuries (like lacerations and fractures) for which tobacco abstinence may aid wound healing.[8-10] Hence the ED visit represents an opportune time to discuss patients' tobacco use, its relevance to their current visit, and a moment to initiate treatment and aftercare.[11]

Our group has recently shown the efficacy of a multicomponent intervention that includes behavioral and pharmacologic therapies in promoting tobacco abstinence among ED smokers.[10] Our model adapts the treatment paradigm known as Screening, Brief Intervention, and Referral to Treatment (SBIRT).[12] The components of our intervention were: an adaptation of motivational interviewing (MI), initiation of nicotine replacement therapy (NRT) in the ED, with provision of a 6-week supply, referral to the state smokers' telephone quitline (QL), provision of a smoking cessation brochure, and a booster phone call 3 days after enrollment. Another recent pilot study of ours showed the feasibility and potential efficacy of ED-initiated short-message-service (SMS) texting for tobacco dependence treatment.

One limitation of our work is that we cannot disentangle the contribution to abstinence of the individual components of the intervention. We assume that each is important, but we cannot model their contributions, or whether important interactions exist. It is therefore important to identify the most clinically effective, and cost effective components, to create an intervention that can be delivered in real-world ED settings.

To that end, we propose to study the effect of our intervention components using a new, innovative methodology: the Multiple Optimization Strategy (MOST).[13-17] The MOST approach, developed by Collins (a consultant on this proposal), is an iterative process that involves testing intervention components in a full- or reduced-factorial design, examining the effects of each, and assembling those components found to be effective within a fixed cost

constraint into a package, which is then tested in a traditional randomized clinical trial. MOST has been particularly useful in designing interventions to treat tobacco dependence.[17,18]

Hence, the goal of this proposal is to conduct a factorial trial, in the ED, of the 4 key components of our intervention package—motivational interviewing, nicotine replacement therapy (NRT), QL referral and texting. We will then identify the clinically effective components, subject to cost effectiveness and qualitative analyses, and assemble a multicomponent, generalizable package to be tested in a future clinical trial.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

RESEARCH STRATEGY:

A. SIGNIFICANCE

1. Millions of Americans smoke. Smoking remains the leading cause of preventable death and illness in the United States, causing 480,000 deaths per year.[1] In 2012, $289 billion in direct and indirect costs were associated with tobacco use. In 2009, US adults had approximately 14 million major medical conditions attributable to smoking.[19] In 2012, 18.1% of Americans smoked,[2] still far short of the 12% prevalence projected by the Healthy People 2020 goals.[3] Certainly, much progress has been made. However, after half a century of research, regulation, policy advances, drug development, public service campaigns, and litigation, it is apparent that smoking has increasingly become an addiction that disproportionately affects the medically disadvantaged: those with low income or low education, the mentally ill, and individuals with other substance use disorders. These are among the groups identified in a 2006 NIH State-of-the-Science conference as those most in need of advances in treatment and treatment engagement.[4]

2. Urgent need for interventions with better reach to low SES populations. Tobacco dependence is traditionally treated by primary care practitioners. However, office-based tobacco dependence treatment with medication or counseling is relatively infrequent.[20] Fortunately, hospital EDs are ideal clinical venues in which to identify and treat the lower socioeconomic status (SES) groups mentioned previously. In 2011, nearly half of all US ED visits were made by patients with Medicaid, Children's Health Insurance Plan (31.8%) or no insurance (16.0%).[5] There is an urgent need to improve the reach of tobacco dependence treatment offered to these smokers. The interventions need to be scalable and practical. Dissemination and implementation research in emergency care settings is a focus of our work.[21]

3. Smokers use emergency departments (EDs) frequently. Patients who use EDs exhibit more risky health behaviors than others.[22] Smoking is no different. Numerous surveys from the 1990s found that ED patients, or parents of children in the pediatric ED, had prevalence rates of smoking in excess of 40%.[7,23,24] Even now, with reduced prevalence rates, ED patients continue to smoke more than the general population, often present with a tobacco-related problem, and are well-positioned for the "teachable moment."[11]

4. Texting shows promise as a smoking cessation aid. A growing body of literature, including a *Cochrane meta-analysis*, attests to the efficacy of texting as primary or adjunctive treatment method for smoking cessation tobacco dependence.[25-28] In 2011, the Guide to Community Preventive Services in the US added mobile programs for smoking cessation to its list of "recommended" treatments for smoking cessation.[29] A pilot study conducted by our group, the first to use texting for smoking in an ED, found the texting intervention in tandem with

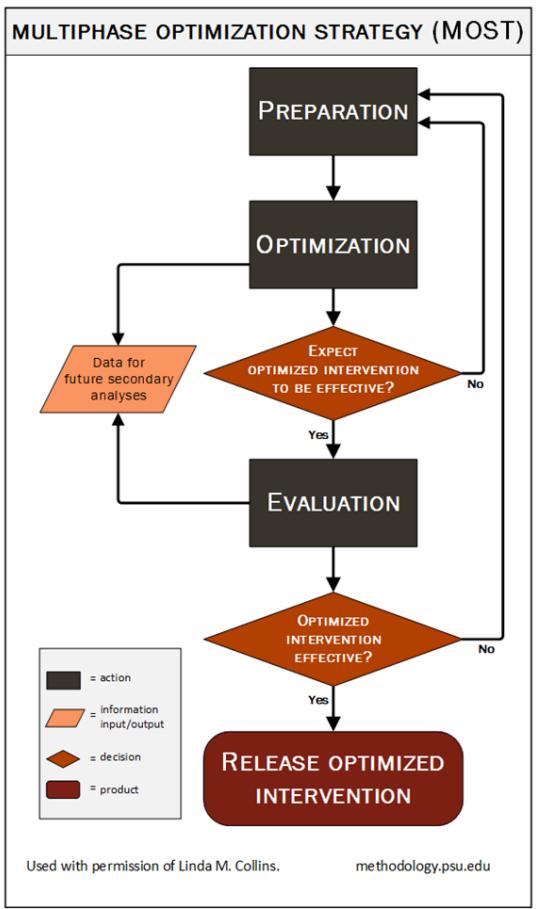
nicotine replacement and quitline referral was feasible, well-accepted by patients, and efficacious . In combination with nicotine replacement and quitline referral, texting showed evidence of efficacy, as measured by self-reported abstinence at 1 and 3 months. Results are given in Section C.2.

5. ED patients, including smokers, own cellphones. Because smokers are disproportionately of lower socioeconomic status (SES), it is important to note that they do, in fact, have widespread access to cellphones. A recent survey by our group of 5539 adult patients in 3 high volume, urban EDs found that 4758 (85.9%) owned cellphones.[30] Of the cell owners, 3469 (72.9%) had texting capability. A separate study by our group of low-income ED smokers found that, of 563 smokers insured by Medicaid or uninsured, 515 (91.5%) had cellphones (presented at 2014 meeting of the Society for Research on Nicotine and Tobacco). Two-thirds of the cell owners had monthly calling plans offering **unlimited** minutes. Hence, even though smokers who visit EDs are disproportionately low-income, most have cellphones offering texting, with unlimited minutes.

6. Advent of STIR: Screening, Treatment Initiation, and Referral. A large but heterogenous body of evidence supports the efficacy of Screening, Brief Intervention, and Referral to Treatment (SBIRT) to reduce unsafe levels of drinking.[31] SBIRT adapts principles of motivational interviewing[32] to evaluate and treat individuals with risky health behaviors, and refer them for aftercare.[12] It has been endorsed by the Substance Abuse and Mental Health Services Administration and the American College of Surgeons to assess for alcohol use in injured patients.[33,34] We have adapted SBIRT for use in the ED with smokers. An important modification is that we begin nicotine replacement medication during the index ED visit—in contrast to standard approaches, in which smokers set a "quit date" 2 or 3 weeks after treatment initiation.[35] We call this approach Screening, Treatment Initiation, and Referral (STIR). Our group at Yale has used STIR to reduce opioid use by the ED-based initiation of buprenorphine, *as reported in JAMA*.[36] STIR jump-starts the process of behavioral change by incorporating FDA-approved pharmacologic treatment into standard behavioral approaches.

7. Integration of quitlines and texting services. Increasingly, state-run quitlines are offering texting services, in addition to traditional telephone-based counseling, print materials, starter doses of NRT, and web-based services.[37] In 2012, 13 state quitlines offered texting;[38] now, Connecticut does too. Callers to quitlines who receive both services report higher levels of satisfaction with the service.[37] With the growing integration of referrals to quitlines into electronic medical records,[39] it will become increasingly easy for providers to refer patients to these evidence-based, widely available forms of behavioral counseling for tobacco dependence.

Figure 1.



8. Promising modality to reach low SES populations. Because of widespread ownership and use of cellphones among low socioeconomic status (SES) groups, quitlines and texting programs hold great promise as treatment modalities with wide reach. Cultural adaptation of quitline and texting content may provide a cost-effective, clinically effective way to reach smokers,[26,40] who increasingly belong to low SES populations.

9. Use of innovative study design: Multiple Optimization Strategies (MOST). *It is common to treat behavioral disorders and addictions with multi-*

component approaches. Given the complex behavioral, genetic, physiologic, and environmental factors that mediate disorders such as addiction, it is perhaps unsurprising that combinations of treatments often work better than monotherapy. Traditional approaches to assess efficacy typically involve a two- or more arm randomized trial that tests a package of interventions against control, or usual care. An important shortcoming of this approach is that it does not enable the investigator to disaggregate the effects of individual interventions, or examine whether important interactions exist between interventions.

A new approach to understand the effects of individual interventions, and then test them in a package, is the Multiple Optimization Strategy (MOST) (Fig. 1). The MOST design, developed by Collins (a consultant on this proposal), is an iterative process that often employs a factorial design (Optimization) followed by a traditional randomized trial (Evaluation), that allows investigators to efficiently identify efficacious components of an intervention, subject to a cost constraint, and combine them in a package to be tested in a follow-on trial. *Our group's* work in ED-initiated tobacco dependence treatment done to date would constitute the Preparation phase. MOST has been used in a number of smoking cessation trials,[18,41-43] but not in the ED. MOST borrows two principles from engineering: (1) the *resource management* principle, which says that research resources should be managed strategically to maximize information gain in a timely fashion, and (2) continuous optimization, which says that a new cycle of research should begin soon after conclusion of the previous cycle, employing the information gained from that cycle.[43]

Our study will use a full 2^4 (i.e. 16-arm) factorial design to evaluate the effects of 4 intervention components at a fraction of the cost, using one-fourth of the subjects it would take to conduct 4 individual experiments to evaluate each component separately.

B. INNOVATION

This proposal offers innovation in a number of fronts: (1) This is the **first** study to assess the efficacy of the *individual components* of ED-initiated tobacco dependence treatment; (2) This is the **first** ED-based study to use the MOST clinical trial methodology; (3) This is the **first** study in the ED of mobile health technology for tobacco dependence treatment; (4) Our treatment paradigm initiates nicotine replacement therapy at the **time of enrollment**, without the traditional 2-3 week period prior to a formal "quit date;" (5) To identify intervention components to be assessed in a future clinical trial, we will use a **mixed-methods** approach that incorporates measures of clinical efficacy, cost-effectiveness, and feasibility/acceptability of the interventions to providers and subjects.

APPROACH

C. PRELIMINARY STUDIES

1. SBIRT + NRT. The objective of this study was to examine the efficacy of an intervention incorporating motivational interviewing, nicotine replacement, and quitline referral for *low-income* adult smokers in an ED. Methods: A two-arm randomized clinical trial conducted from October 2010-December 2012, at a 90,000 visit/year urban ED. Eligible subjects were age 18 years or older who smoked and were self-pay or had Medicaid. Intervention subjects received a motivational interview by a trained research assistant, 6 weeks of nicotine patches and gum initiated in the ED, a faxed referral to the state smokers' quitline, a booster call, and a brochure. Control subjects received the brochure, which provided quitline information. The primary outcome was biochemically confirmed tobacco abstinence at 3 months. Of 778 enrolled subjects, 774 (99.5%) were alive at 3 months. The prevalence of biochemically confirmed abstinence was 12.2% (47/386) in the intervention arm vs. 4.9% (19/388) in the control arm, for a difference in quit rates of 7.3% (95% CI 3.2%, 11.5%). The proportion of subjects using quitline services in the intervention and control arms was, respectively, 32.0% (124/386) and 18.7% (73/388) (P<0.0001). Thus, an intensive intervention improved tobacco abstinence rates

in low-income ED smokers. Because approximately 20 million smokers, many of whom are low-income, visit US EDs annually, these results suggest ED-initiated treatment may be an effective technique to treat this group of smokers.

Table 1 shows the uptake of the various components of our intervention in the two arms. For all components other than the brochure, intervention subjects used or received more components. We are not, however, able to disentangle the individual effects of these components, or their potential interactions. That is the goal and the rationale of this proposed study.

Table 1. Component utilization.

	Intervention	*Control*
Abstinent	*Meds 100% (80%)** *BNI 100%* *QL 100% (25%)*** *Booster 79%* *Brochure 100%*	*Meds 31%* *BNI 0%* *QL 23%* *Booster 0%* *Brochure 100%*
Not abstinent	*Meds 100% (75%)** *BNI 100%* *QL 100% (42%)*** *Booster 72%* *Brochure 100%*	*Meds 70%* *BNI 0%* *QL 24%* *Booster 0%* *Brochure 100%*

**Numbers in parentheses refer to subject self-reported use of intervention*
***Numbers in parentheses are data from CT QL*

Relevance: Our group has demonstrated the efficacy of a multicomponent ED-initiated intervention for tobacco control, one that targeted low-income smokers. We have the ability to conduct a large-scale randomized clinical trial in the ED and recruit adequate numbers of subjects in a timely fashion. *This study is currently being examined by the Cochrane group for inclusion in a review of combined pharmacologic and behavioral approaches for smoking cessation.*

2. Texting pilot. The objective of this study was to assess the feasibility of an ED-initiated program of tobacco dependence treatment that employs a publicly available text messaging program. Smokers age 18 or older were randomized to intervention or control arms. Control subjects received a brochure describing the state smokers' quitline. Intervention subjects received the brochure, 4 weeks of patches and gum, with the initial dose administered in the ED, a faxed referral to the quitline, and enrollment in SmokefreeTXT, a free SMS-messaging service developed by the National Cancer Institute. SmokefreeTXT delivered 28 days of messages, 2-5 messages/day. Message content adapts principles of cognitive behavioral therapy. Messages are interactive; some ask subjects to provide data on current smoking, mood or craving, using Ecological Momentary Assessment (EMA).[44] Follow-up was by self-reported phone call. We enrolled 60 subjects in May 2014. Of all subjects, 30 (50%) were female, 27 (45%) were white, 33 (55%) nonwhite, mean age 40 years (SD 11), and insurance coverage of Medicaid, self-pay, or other, respectively, of 78%, 8%, 14%. All intervention subjects used the texting program, with 24/30 (80%) using the program for all 28 days; 6 subjects opted out at some point. *This pilot study showed evidence of efficacy*: at one month, 14/30 subjects (47%) in the intervention arm reported tobacco abstinence, vs. 3/30 (10%) in the control arm (P=0.003). At 3 months, the self-reported abstinence rates in the intervention and control arms was, respectively, 9/30 (30%) and 4/30 (13%) (P=0.21). Thus, we found that a texting program, combined with pharmacotherapy and a quitline referral, shows promise to promote tobacco abstinence in ED smokers.

Relevance: This study is the first to demonstrate the feasibility of an ED-initiated tobacco dependence treatment intervention that includes texting. Although we cannot disaggregate the impact of texting from the other components, we have some evidence of effect, and have shown the feasibility of ED-initiated texting.

3. Qualitative research. In order to gain a deeper understanding of subjects' attitudes about the acceptability and utility of SmokeFreeTXT, we analyzed qualitative data from 25 subjects who had been randomized to the intervention arm. We developed a guide for the telephone interviews (see Appendix) and a preliminary coding schema covering the domains of

usability and acceptability of the program. The guide included several close-ended items with Likert response formats to assess subjects' attitudes about the number and spacing of messages per day, clarity of wording, and helpfulness of the program. Finally, subjects rated 11 specific messages from the program, some of which the research team considered to be potentially problematic for our population (e.g., "dated," unrealistic for subjects with limited financial resources).

All interviews were audio-recorded and transcribed. Data were analyzed thematically and iteratively. To expand and adapt the original conceptual framework, "negative" instances (i.e., comparative analysis that may not fit initial constructs) were also sought.

Most subjects viewed the program as helpful. Common themes included having a sense of being emotionally supported in their efforts to quit, feeling "personally understood" by the program, and that the messages were non-judgmental. The number and spacing of messages per day was positively received; subjects considered the language to be very easily understood. Most subjects appeared to want to receive 2-4 messages per day, although some subjects preferred substantially more (i.e., 8-10 per day). Two important themes to emerge concerning the timing of when to receive messages were convenience and at "trigger" times. Tailoring the timing to fit subjects' daily routines appears to be important to consider in further refinement of the program.

Relevance: Our group has the ability and experience to conduct mixed methods analyses, in order to identify facilitators and barriers to intervention implementation. This allows us to design interventions that are likely to be disseminated, implemented, and sustained across the diverse group of US EDs.

4. Other investigators. Benjamin Toll, PhD, is *Associate Professor of Public Health Sciences, and Chief of Tobacco Cessation and Health Behaviors at the Hollings Cancer Center and the Medical University of South Carolina. His work examines the effects of message framing on the efficacy of quitline interventions. Drs. Toll and Bernstein continue their collaboration of 6+ years, even with Dr. Toll's recent move from Yale to MUSC. Dr. Toll phones in to weekly meetings of Dr. Bernstein's research group, and continues to co-author papers.* **James Dziura, PhD**, is Associate Professor of Emergency Medicine, Associate Director of the Yale Center for Analytic Sciences and Biostatistics Core of the Yale Center for Clinical Investigation, the institution's CTSA and Deputy Director of the Yale Data Coordinating Center. Dr. Dziura has collaborated with Dr. Bernstein for 4 years, and offers expertise in the design, coordination and quantitative analysis of clinical trials. ***Michael Pantalon, PhD****, is a clinical psychologist and Research Scientist in Emergency Medicine at Yale. Dr. Pantalon will train the study's research assistants to perform the brief negotiation interview, and review their taped interviews biweekly. He performed a similar function in Dr. Bernstein's prior ED trial*. **Linda Collins, PhD**, is Distinguished Professor of Human Development and Family Studies, and Professor of Statistics at Pennsylvania State University, and Director of the school's Methodology Center. She pioneered the development and use of the Multiple Optimization Strategy (MOST) design for clinical trials. **Lorien Abroms, ScD, MA**, is Associate Professor of Prevention and Community Health at George Washington University's School of Public Health and Health Services, and Director of George Washington University's mHealth Collaborative. She pioneered the development and use of telephone-based texting to treat tobacco dependence. **Ted Miller, PhD**, is a Senior Scientist and health economist at the Pacific Institute for Research and Evaluation and frequent collaborator with Yale emergency physicians, including Dr. Bernstein, on cost-effectiveness studies. **Lauretta Grau, PhD**, is a Senior Research Scientist in the School of Public Health with rich experience in conducting qualitative research in individuals with substance use disorders, HIV, and hepatitis. She has collaborated with Dr. Bernstein for the past year on a qualitative analysis of the texting program to be used in this trial.Katrina Vickerman**, PhD**, is a Research Scientist with Consumer Wellness Solutions,

Inc. (formerly Alere, Inc.) who is an expert on the use of tobacco quitlines. She has collaborated with Dr. Bernstein on several projects.

D. OVERALL APPROACH

1. Overview. We propose to optimize the identification and treatment of adult smokers seen in a hospital ED. To do this we will employ the Multiple Optimization Strategy to develop a multicomponent intervention that will consist of some combination of the following: (1) a Brief Negotiation Interview (BNI, a variant of a motivational interview[32]), delivered by a trained research assistant; (2) provision of 6 weeks of nicotine patches and gum to the research participant, with application of the first patch in the ED; (3) active referral to the Connecticut Smokers' Quitline; and (4) enrollment in the SmokefreeTXT short-messaging service (SMS) texting program for mobile phones. Using MOST principles, the first phase of the study will use a 2x2x2x2 full-factorial design to identify the components most likely to be efficacious in combination. Although the factorial design requires the allocation of participants to 16 different combinations of the 4 components (Table 1), evaluation of each individual component is performed comparing all of those receiving a component to all of those not receiving a component, making this an efficient design. For instance, evaluation of the BNI component will compare those randomized to arms 1 through 8 to those in arms 9 to 16.The second phase will consist of designing and proposing a 2-arm randomized clinical trial comparing the efficacy of the multicomponent intervention package to usual care; this will be conducted in a **future** application.

Table 2. Arms of the trial.
Green = condition is offered.
Red = condition is not.

Arm	BNI	NRT	QL	Text
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				

BNI = Brief Negotiated Interview.
NRT=Nicotine Replacement Therapy
QL=Quitline referral
Text=Smoke-Free Text

The primary outcome measure is the proportion of smokers in each group abstinent at 3 months (verified by exhaled carbon monoxide). Secondary outcomes include the cost effectiveness of the intervention, as well as acceptability/feasibility. The BNI will be specified in a manual and provided to research assistants (RAs), who will be trained by experienced study personnel. Patients will be screened for eligibility and enrolled by these RAs, with the proviso that the RA who enrolls a participant will not be the RA who performs the BNI.

2. Setting. New Haven, Connecticut, is a poor city; 24.4% of its 350,000 residents live in poverty. YNHH is a tertiary care center. In 2013, women represented approximately 55% of the ED population; the mean age of
ED adults was 41 years. The racial mix of our patients reflects that of New Haven: 65% White, not Hispanic; 23% African-American, not Hispanic, 10% Hispanic; 2% other. Payor status for ED smokers is approximately 55% Medicaid, 5% Medicare, 30% private insurance, and 10% self-pay.

Number of smokers. Based on work from prior studies at the YNHH ED, and assuming a conservative prevalence rate of smoking (at least 5 cigarettes/day) of 20% among uninsured or Medicaid patients, we estimate the YNHH ED treats 15,200 potentially eligible patients annually. (This estimate is conservative because low-income individuals smoke more than others. Data from the 2006 National Health Interview Survey found a smoking prevalence rate of 30.6%

among individuals with household incomes below the federal poverty level, compared to 20.4% for those with household incomes above the poverty level.[45])

3. Participants. Inclusion criteria. Patients who present to the adult ED at Yale-New Haven Hospital (YNHH) will be eligible for the study if they are: (1) 18 years or older (2) have smoked >= 100 cigarettes lifetime (3) describe themselves as every or some day smokers (4) smoke at least 5 cigarettes/day (5) own a cellphone with texting capability, and (6) are able to give written informed consent (a draft is in the Appendix).
Exclusion criteria. Patients will be excluded for: (1) Inability to read or understand English; (2) currently receiving formal tobacco dependence treatment; (3) life-threatening or unstable medical, surgical, or psychobehavioral condition; (4) unable to provide at least one collateral contact; (5) live out-of-state; (6) leaving the ED against medical advice (7) *being pregnant (self-report or urine testing),* nursing, or trying to conceive.

4. Entry into study and Randomization. *Subjects will be recruited during all days of the week, from 7a-11p.* Potential subjects will meet with a research assistant (RA) to be evaluated for eligibility. Patients will be asked for verbal consent to complete the 2-item tobacco screener used by the Behavioral Risk Factor Surveillance System (Do you currently smoke every day, some days, or not at all? Have you had more than 100 cigarettes in your lifetime?). Patients who report smoking < 5 cigarettes/day will not be enrolled, but will be given a handout recommending that they abstain from smoking, contact their primary care provider, and consider calling the quitline. Individuals *who meet* inclusion and exclusion criteria and consent to participate will have their baseline assessments performed, and then will be randomized to one of 16 combinations of components (Table 1). To assure equal intervention allocation and concealment of intervention allocation a random permuted block sequence will be generated and intervention assignments distributed through the clinical trial management system.

5. Components of the Intervention. Our previous work employed a multicomponent approach to ED-initiated tobacco treatment, which used both pharmacologic and behavioral approaches. All components are evidence-based, and cited in the 2008 PHS clinical practice guideline, with the exception of the newest approach, SMS texting. Below we discuss these components, the rationale for each, and supportive evidence. Our intent is to use the MOST approach to identify the individual contributions of these components, and assemble them into an intervention that is effective, efficient, and scalable.

Brief negotiated interview (BNI). Brief Negotiated Intervention (BNI) is a manual-guided therapy that is designed to be feasible in the ED setting. The BNI manual for this study is based on one that we used in our previous trial. The purpose of the BNI is to assist patients in recognizing and changing their tobacco use. It combines techniques based on motivational interviewing and a stage-model of change.[32,46] The main goals of the interview are to decrease subjects' ambivalence about engaging in tobacco dependence treatment and accepting ED-initiated treatment, including NRT, texting, and QL referral.

The BNI will be delivered by a trained research assistant (RA), a bachelor's-level individual, who will audiotape the encounters. Tapes will be reviewed biweekly by the RAs and Dr. Pantalon, to assess fidelity to protocol. In our prior work, the BNIs average 10-15 minutes in length. RAs will receive 10 hours of training by Dr. Pantalon in our manualized BNI, and by Dr. Bernstein in nicotine replacement pharmacotherapy. Next, RAs will role-play patient scenarios with Dr. Pantalon, followed by 1 week of shadowing an experienced RA performing BNIs on ED patients. We have used these procedures in all prior studies of ED SBIRT.

If, during the BNI or other interactions, the subject discloses to the RA risky behaviors such as suicidality, intimate partner violence, or use of other substances, the RA will notify the treating ED physician.

Nicotine gum and patch, with initial dose applied in the ED. Subjects randomized to NRT will receive 6 weeks of patches (42 count) and gum (300 pieces of 2mg), free of charge. *All NRT will be given to the subject in a small shopping bag*. NRT dosing is tailored to the patient's score on the Heavy Smoking Index.[47] Patches come in 7, 14 and 21 mg doses. The first patch is applied by an ED nurse during the index visit. This allows us to demonstrate to the subject how to use the patch, its ease of use, and acceptability. It does bypass the traditional model of setting a quit date, although subjects may continue to reduce their tobacco use while using NRT. In our previous study, this approach was accepted enthusiastically by subjects. We employ combination NRT because of its generally greater efficacy than NRT monotherapy in promoting tobacco abstinence.[48]

Texting. We will use the SmokefreeTXT program, developed by NCI. SmokefreeTXT is a text messaging service designed for U.S. adults who are trying to quit smoking. The program provides 24/7 encouragement, advice, and tips to help smokers quit, and stay quit. It is a 6-8 week program. Users receive 1-5 messages per day and can receive additional quit support by texting one of SmokefreeTXT's keywords. The service is free, other than the usual message and data rates per callers' phone plans. SmokefreeTXT has shown evidence of efficacy. A recently completed randomized trial of 4000 smokers found a self-reported quit rate of 20% at 6 months in the texting arms (E. Augustson, personal communication). Subjects received no other interventions.

The SmokefreeTXT library contains about 130 messages. In our pilot, we did some modest tailoring. We deleted texts that seemed less relevant to ED patients (e.g. "Jab, jab, punch! Visit your local gym or YMCA. Try taking boxing classes. Not only is it a great stress reliever but it's also an awesome workout"), and added some that were (e.g. "Remember that you can use the nicotine patch and gum at the same time to manage cravings.") Based on our pilot qualitative work, we may offer additional tailoring, addressing the reason for visit (e.g. asthma attack). ICFI International, the SmokefreeTXT vendor, has worked with us already on tailoring.

Active quitline referral. Connecticut's quitline services, provided by Consumer Wellness Solutions, Inc. (), combine individualized telephone counseling, written materials, and an interactive online program to complement phone-based treatment sessions. Participants receive up to 5 proactive counseling calls, designed to help develop problem-solving and coping skills, secure social support, and design a plan for cessation. Calls are scheduled at convenient times and at relapse-sensitive intervals, up to 50-51 days post-quit. Participants can also call a 1-800 number for additional support between proactive calls. The effectiveness of the Quitline program has been validated by 3 randomized trials[49-51], and several real-world evaluations[52-54]. In our prior study, 32% of subjects in the intervention arm engaged in $\geq$1 call with the QL.

Of note, future versions of Epic may contain functionality allowing the provider to send an electronic referral to the state quitline (mentioned at the Epic fall 2014 Users Group Meeting, attended by this proposal's PI). That said, for now we will still have RAs fax the traditional paper referral form to Consumer Wellness Solutions, Inc., the QL vendor for CT.

Post-visit booster call. In our prior studies, intervention subjects received a phone call 2-3 days after enrollment. The purpose of this call is to remind participants that they are enrolled in a trial, ask if they have questions about their treatment, reaffirm contact information, and thank them for participating. We reach about 70% of the subjects. Our experience suggests that these calls add little to the efficacy of the intervention. They do, however, require manpower and support which might be better spent on other activities, like recruiting. We have therefore decided not to perform booster calls in this proposal.

Smoking cessation brochure. In our work, all participants are provided with a brochure that reviews the health hazards of smoking, and provides the phone number for the state quitline. In Connecticut, this brochure is produced by the State Department of Public Health, printed in English and Spanish, and is available in bulk *at low cost*. We believe that distributing this brochure to all study participants is a reasonable maneuver for all subjects. That will not allow

us, of course, to isolate any discrete effect of the brochure on tobacco abstinence. In the parlance of MOST designs, that is known as "aliasing."[43] We believe this is an acceptable approach.

6. Measures. Overview. We will assess a range of pretreatment subject characteristics, process measures and treatment outcomes (Table 2). Baseline assessments are designed to ensure that patients meet eligibility criteria and that important predictor variables are assessed. Process measures include utilization of health care and nicotine dependence treatment services, and adherence to the treatment manual and competence in performing the treatments. Primary outcome measures include tobacco use; secondary measures include engagement in treatment, health care service utilization, and cost indicators. Outcomes will be assessed from multiple sources, including patient self-report of treatment engagement, tobacco use, and objective measures such as Quitline verification regarding patient contact and exhaled carbon monoxide testing.

Formal follow-up assessments are planned at 1 and 3 months. The 3-month follow-up is designed to capture our primary outcome of tobacco abstinence. It is plausible that the effect of the BNI may be short lived and therefore we have scheduled an early initial follow-up (e.g., 30 days). To decrease respondent burden the 1 and 3 month assessments will be collected via telephone. Subjects self-reporting tobacco abstinence at 3 months will be asked to return to the ED to measure exhaled carbon monoxide, a validated measure of tobacco abstinence. In our prior ED study, we found that low-income subjects were easier to reach by phone earlier in the month rather than later, perhaps because of loss of cellphone service due to financial difficulties. Therefore, we will "front-load" our follow-up calls in the first half of each month.[55]

Baseline Assessments

Baseline instruments have been selected for their ability to test the specific study aims, for brevity, and ease of administration. Demographic and locator information in all groups will be collected by face-to-face interview.

a. Demographic information: includes age, sex, racial/ethnic group, educational level and insurance status.

b. Exhaled carbon monoxide (CO). All patients will receive biochemical verification of smoking status, via point-of-care measurement of exhaled CO. Testing will be performed by a trained research associate with the Bedfont Micro+® breath CO monitor (Bedfont Scientific Ltd.) Calibration will be performed every 6 months, as recommended, by a research assistant. CO levels will be used to verify clinical equivalence of treatment groups at baseline. Consistent with standard practice, a cutoff of 10 ppm will indicate current smoking.[56]

Table 3. Baseline Assessments, Outcome and Process Measures

INSTRUMENT	**Base-line**	**Month**	
		1	**3**
BASELINE AND OUTCOME MEASURES			
Intake History/Patient Demographics	X		
Exhaled carbon monoxide level	X		X
PHQ-2 Depression Screen	X		
Treatment engagement		X	X
Causal attribution scales	X		
Wisconsin Predicting Patients' Relapse	X	X	X

Questionnaire			
Heaviness of Smoking Index	X	X	X
Rapid Alcohol Problem Screen	X		X
Rapid Drug Problem Screen	X		X
Self-report of tobacco use	X	X	X
PROCESS/IMPLEMENTATION MEASURES			
Treatment Service Review (TSR)		X	X

c. The Patient Health Questionnaire-2 (PHQ-2) will be used to assess depressive symptoms.[57] This 2-item scale, which rates the frequency and duration of depressive symptoms during the past two weeks, has shown excellent reliability and validity. Scores can range from 0-6, with scores of 1-4 indicative of possible depression and scores of 5-6 indicating probable depression.

d. Causal attribution assessments.[11] Sentinel health events may be associated with changes in smoking behavior. These may include a visit to an ED for a tobacco-related illness, hospital admission, or surgery. Patients who perceive their acute health events as related to tobacco use are more likely to quit, as we found in our pilot trial. We will therefore assess patients' beliefs re: the proximate reasons for their ED visit, using a 2-item measure co-developed by Dr. Bernstein.

e. Wisconsin Predicting Patients' Relapse Questionnaire (WI-PREPARE).[58] This 7-item scale will be used to assess patient's likelihood of a relapse to smoking, after the ED visit. Two items of the WI-PREPARE, assessing time to first cigarette and daily consumption, constitute the Heavy Smoking Index (HSI), a subscale of the Fagerström Test for Nicotine Dependence (FTND).[47,59] The HSI, a measure of the severity of nicotine dependence, will be used to guide the dosing of NRT.

f. Biochemical assessment. Exhaled carbon monoxide (CO) levels will be measured for each enrollee with the Bedfont Smokerlyzer. CO will be measured again at 3 months for subjects self-reporting tobacco abstinence. Subjects endorsing abstinence by phone will be asked to return to the ED, or a mutually convenient location in New Haven, for CO measurement. *In our last trial, 92/97 (94%) such subjects returned.*

h. Rapid Alcohol Problems Screen (RAPS). The RAPS is a 4-item tool designed specifically for detecting problematic alcohol use in medical settings, and it has been well-validated for use in the ED setting.[62,63] A "yes" response on any of the items places the participant in the "likely" group. The RAPS has demonstrated good reliability and validity when validated against ICD-10 and DSM-IV criteria for alcohol abuse or dependence, with an average sensitivity of 93% and specificity of 87%. It generally outperforms other alcohol screening measures like the CAGE and the AUDIT in terms of test characteristics.[63]

i. Rapid Drug Problems Screen (RDPS). The RDPS is a 4-item tool patterned after the RAPS.[64] It is designed specifically for detecting drug use within medical settings. It is a newer instrument and has less well-established test characteristics than the RAPS, but preliminary data for use in the ED setting are promising.[64] A "yes" response on any of the items places the participant in the "likely" group. For males, the RDPS has demonstrated good test characteristics when validated against ICD-10 and DSM-IV criteria for drug abuse or dependence, with a sensitivity of 93% and specificity of 96%. The validation study did not have enough subjects to adequately assess the RDPS' test characteristics among females.

Process measures

a. The Treatment Service Review (TSR),[65] a brief, structured interview, will be administered to collect information on the type and amount of services received by subjects. This includes ED visits, hospitalizations, primary medical care visits, and self-help sources of support (e.g. quitline, web services). The TSR will be supplemented with questions on the use of smoking cessation medications.

b. Adherence to the BNI manual: All BNIs will be audiotaped and reviewed by Dr. Pantalon and the RAs, to assess time with the patient, material reviewed, and proficiency of the provider at each session.

Outcome measures

a. Treatment engagement will be assessed by subject self-report, reports from Consumer Wellness Solutions, Inc. on QL use, and reports from ICFI International on texting engagement. Patients will be considered engaged in treatment if at 30-days after randomization the patient reports currently receiving care in a treatment program that addresses the patient's nicotine dependence.

b. Self-report tobacco use at 1 and 3 months. Several measures will be assessed, as recommended by an expert panel.[66] The primary endpoint is 7-day point prevalence abstinence; secondary endpoints are 30-day and continuous abstinence. A time-line follow-back (TLFB) technique[67,68] will be used for all endpoints.

c. Exhaled carbon monoxide: will be collected in-personat baseline and in-person at 3 months, for subjects self-reporting abstinence. *In our prior study, 94% of self-reported abstainers returned for testing.*

d. Use of cessation medications and services. Quitline use, NRT use, use of other pharmacotherapies such as bupropion and varenicline will be assessed by self-report and fax reports from the CT quitline.

e. The TSR will be administered by a research assistant at 1 and 3 months to assess changes in use of tobacco treatment services, including the Quitline, medical services and medications.

11. Alternative strategies and methodologic considerations.

Why not perform the multicomponent randomized clinical trial shortly after completing the factorial trial, within the traditional 5-year duration of an R01? We explored a number of possible effect sizes, power and sample size calculations that might have allowed that. We chose not to do so for several reasons. First, it takes up to a year after completing enrollment in the factorial trial to identify components for the RCT. The time is spent completing follow-up (3 months in this proposal), gathering and analyzing the economic data, performing the cost effectiveness analyses, analyzing the qualitative data with subjects, and then planning the RCT. Given the effect size chosen for the factorial design, our expected accrual rate, and the need for the post-study analyses just described, we felt it most prudent to perform the factorial study as a stand-alone application, with a subsequent application for the follow-on randomized trial of the newly assembled package. *That said, we are able to complete the proposed work in a cost-sensitive, accelerated 4-year design.*

Why not follow participants up to 1 year after enrollment? In tobacco treatment trials, participant follow-up commonly lasts 6-12 months. Our prior study followed subjects for 12 months, with the primary endpoint assessed at 3 months. We prefer the 3-month endpoint, with no extension of follow-up, because: (1) For a point-in-time intervention such as ours, the expectation of a treatment effect at 1 year is unrealistic, and probably not clinically sensible; (2) Viewing tobacco dependence as a chronic disease, with alternating periods of abstinence and relapse, is a more realistic model of addiction.[90] In this model, treatment may need to be sustained for longer periods, as it is for other chronic diseases such as hypertension or diabetes. Therefore, one would not expect a single ED-initiated intervention to lead to sustained abstinence; (3) In practical terms, given our sample size, extending follow-up to 1 year would not be feasible in an accelerated l 4-year design.

That said, for our follow-on RCT that will test the complete multicomponent package, we will follow subjects up to 1 year, as part of an exploratory aim and hypothesis.

Why not a fractional factorial design? Our trial is comparable, in number of arms, to other studies done using MOST methods, including those assessing tobacco dependence treatment.[42,43] We considered a fractional design, but were unsure which cells in the 4x4 matrix might be jettisoned. We know little about potential interactions among BNI, NRT, QL, and texting (other than there are additive effects when combining behavioral and pharmacologic modalities[48]). Therefore, our preference is to retain the full factorial design.

How will research staff maintain fidelity to protocol, with a 16-arm trial? We have an experienced group of RAs, and rigorous procedures for training and assessing fidelity to protocol. Intervention components are familiar to our study staff, physicians, nurses, and research pharmacist. All data, including assessments and treatment assignment, are captured using tablet computers which the RAs store in the ED. RAs are trained by a psychologist skilled in behavioral interventions, who meets with them biweekly to review taped subject encounters. RAs will first enroll a small number of subjects in a run-in period, to test our assessments and procedures, as we have done previously. We have an on-site automated, electronic medication dispensing system (Pyxis) dedicated to research, to store the NRT, with which our nurses are familiar from our prior trial. The project manager, who has worked with the PI for 5 years, will oversee all enrollments on a daily basis.

Is this generalizable? Yes. The *raison d'être* of MOST is to design interventions that can be implemented broadly. All intervention components can be done now, at many EDs. Brief negotiated interview techniques are increasingly taught to medical students and EM residents; ED physicians can, and do, initiate NRT; quitline referrals are occasionally made; and texting is increasingly a focus of study for a variety of ED interventions in the domains of adherence and follow-up care.[91-94] Of note, the 2015 version of the Epic EMR is likely to offer an electronic referral to tobacco quitlines; that will certainly facilitate our proposed intervention.

12. Next steps. In a follow-on study, we will perform a two-arm trial to test the efficacy of our newly assembled multicomponent package. The trial will be conducted at our ED at Yale-New Haven Hospital. Work beyond that will consist of a dissemination and implementation strategy to move the package into other EDs.

4. Genetic Testing N/A ☒

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

   Adults age 18 or over, who present to the adult ED at Yale New Haven Hospital (YNHH).

6. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion criteria. Patients who present to the adult ED at YNHH will be eligible for the study if they are: (1) 18 years or older (2) have smoked >= 100 cigarettes lifetime (3) describe themselves as every or some day smokers (4) smoke at least 5 cigarettes/day (5) own a cellphone with texting capability, and (6) are able to give written informed consent (a draft is in the Appendix).

Exclusion criteria. Patients will be excluded for: (1) Inability to read or understand English; (2) currently receiving formal tobacco dependence treatment; (3) life-threatening or unstable medical, surgical, or psychobehavioral condition; (4) unable to provide at least one collateral contact; (5) live out-of-state; (6) leaving the ED against medical advice (7) being pregnant (self-report or urine testing), nursing, or trying to conceive.

8. How will **eligibility** be determined, and by whom? Trained research assistants will determine eligibility by first querying the medical records of patients currently being treated in the ED. Potential subjects will meet with a research assistant (RA) to be evaluated for eligibility. Patients will be asked for verbal consent to complete the 2-item tobacco screener used by the Behavioral Risk Factor Surveillance System (Do you currently smoke every day, some days, or not at all? Have you had more than 100 cigarettes in your lifetime?).

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Overall Risks

Because the procedures herein involve accepted forms of treatment interventions, rating scales and assessments, self-reports, and structured interviews, we foresee no special risks. The instruments have been used in similar projects in the past with no ill effects. The potential risks in this study are related to 1) nicotine replacement, 2) ratings scales and assessments, 3) breath collection, and 4) loss of confidentiality. The use of nicotine replacement involves minimal risk, and most risks are related to the use of the patch and discomfort at the site and difficulty sleeping. Blood samples may be collected as part of the standard of care in the ED; these results will not be utilized for this study. Breath samples are collected for research purposes and should add no risks other than those normally associated with the collection procedure. The rating scales and structured assessments are all non-invasive and have been utilized in clinical studies with no known negative outcomes and should also add no risks to subjects, as our past experience indicates. The main risk associated with the study is the possibility that confidential information obtained during the study will be disclosed. All efforts will be made to protect subjects' confidentiality. The alternative to participation is for a potential subject to decide NOT to participate.

Risks Associated with Nicotine Replacement

Under order of the treating physician, consenting patients will receive their first NRT product (patch and/or gum) in the ED, and a "starter kit" to take home which will include a 6-week supply of medication. Smokers admitted to inpatient units will have their treating physician contacted by the study team, to encourage continuation of pharmacotherapy while in hospital. The study team will follow up with admitted patients who, when, discharged, will receive sufficient medication to fulfill a 6-week course of treatment.

There are minor, non-life-threatening risks associated with using the gum. The subject could use too much, or chew too quickly, which might lead to symptoms of nicotine toxicity. This could also occur if the subject smokes while using the patch or gum. Symptoms associated with nicotine "overdose" include cold sweats, fainting, confusion, and pounding heart. Toxicity resolves in several hours. Cases of nicotine toxicity are extremely rare. In terms of the patch, nicotine continues to enter the bloodstream for several hours after removing it, as it leaches through the skin, so smoking within 12 hours of removing the patch is strongly discouraged One of the most common side effects of the patch is a localized skin rash due to a reaction to the adhesive on the patch or a reaction to the nicotine. A topical salve (such as 1% hydrocortisone cream) can relieve the discomfort. The second most common side effect is sleep disturbance. This side effect is common in people who use the 24-hour patch. Nicotine can lead to vivid, colorful dreams and difficulty sleeping. For this study, the 24-hour patch will be utilized. Switching to a 16-hour patch might alleviate this problem, but it often can result in nicotine cravings. Other potential side effects of NRT include dizziness, insomnia and abdominal discomfort.

Nicotine gum has a peppery taste, which some participants may find unpleasant. (Note that we mitigate this by using mint-flavored gum.) It may cause a tingling sensation when chewed. During the first few days of using the medication, the participant may experience mouth soreness, jaw muscle aches, increased saliva production, indigestion, or headache. These effects should dissipate over time. There are some risks associated with chewing the gum too fast, in that it can cause lightheadedness, dizziness, hiccups, nausea, vomiting or insomnia. All participants will be asked to notify us if they develop symptoms of too much nicotine in their body.

There is also a very small risk that the subject could have an allergic reaction to the drug in either product. If this occurs in the ED, the RA will notify the treating physician at once. If this occurs after discharge, the subject will be directed to seek immediate medical attention. Symptoms of an allergic reaction include rash, itching, swelling, dizziness, and trouble breathing.

Risks Associated with Breath Collection

Breath Collection - Subjects will have breath samples taken to measure CO to verify clinical equivalence of treatment groups at baseline. Testing will be performed by a trained research associate with the Bedfont Micro+® breath CO monitor (Bedfont Scientific Ltd., Rochester, UK). There are no known risks associated with this test. Subjects exhale into a disposable plastic sterile straw attached to the monitor; there should be no risk of infection.

Risks Associated with Rating Scales and Assessments

Other risks from the rating scales and assessments, self-reports, and interviews are not beyond usual research procedures. Research assessments are all non-invasive, and should add no risk. The major disadvantages are the time taken to complete them and possible breach of confidentiality. Our past experience with these measures indicates that they are acceptable to subjects. Any potential risks (e.g., discussion of upsetting events), however, will be minimized through the use of a trained, experienced Research Associates, supervised by Drs. Bernstein and Pantalon for screening, intervention, and appropriate referrals. In addition, the Yale-New Haven ED has an onsite, adjacent Crisis Intervention Unit (CIU) staffed by attending and resident psychiatrists 24 hours each day which can be accessed if necessary. All adverse events will be immediately reported to the PI by research staff.

Risks Associated with Texting

The text messaging program will serve as a stand-alone health education program for quitting smoking. The program will not interface with the electronic health record, and therefore will be free of additional constraints imposed by HIPAA. Nonetheless, text messaging is not a secure mode of communication. As part of the informed consent process, participants will be informed about the privacy risks associated with text messaging. Participants will also be informed that their interactions with the SmokefreeTXT computer system will be analyzed as a marker for their participation in the program.

Risks Associated with Loss of Confidentiality

Confidentiality of the results are specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the Project Director.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Protections Against Risks

Inclusion and exclusion criteria and the use of a trained Research Assistant will help to avoid the enrollment of subjects into this study who are either ineligible or who would be at greater risk for complications because of neurological, psychiatric, or medical illnesses.

All patient interactions will be conducted in areas that are as private as possible in an ED setting.

Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Computerized subject data will be password protected. All identifiable information will be stored in a locked research cabinet in a locked office. All subjects will be assigned a study subject number. Subsequently, subjects will be identified in encrypted, secured tablet computers accessible only to study RAs only by that number and an encoded version of their initials (i.e., John Doe = JDO). A list of numbers and the corresponding names will be maintained by the Project Director.

Any identifiable information that is obtained in connection with this study will be disclosed only with subject permission or as required by U.S. or State law. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996. We will clearly explain our mandated obligation to report incidents, including suspicion of child or elder abuse or neglect, threats of harm to self and others, and threats of damage to property. Data will only be reported in aggregate. During an audit or program evaluation, representatives from the Yale Human Investigation Committee and from the National Institutes of Health may have access to subject data, but will strictly adhere to the rules of confidentiality. Upon completion of the study, all computerized subject datasets will be de-identified and stored in a password-protected study computer, to which only the PI and study personnel will have access. Any paper files with subject information will remain in locked files in the study office of the Project Director, until they are destroyed, after all analyses are complete and after the federal requisite waiting period (7 years) to maintain records.

Data will be collected using Filemaker for iPad. IPads are encrypted and stored in a locked safe in the RA's locked office in the ED. The iPads are connected to a university-maintained server via an encrypted WiFi connection. This is a live connection; therefore, all data are immediately stored on the secure server. The server is backed up hourly. No ePHI is stored on the iPads.

This system is compliant with HIPAA and regulations for the collection of ePHI. Computers are encrypted with PGP software.

Any information published as a result of the study will be such that it will not permit identification of any subject.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal

Data and Safety Monitoring Plan

Monitoring for data integrity and safety will be the responsibility of the investigators and the Yale Human Investigation Committee (HIC). The principal investigator (PI) will be responsible for monitoring the data, assuring protocol compliance, conducting the safety reviews, and the specified frequency of the reviews at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the PI will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the PI or the HIC have the authority to stop or suspend the study or require modifications.

Based on our prior work, the risks associated with the proposed study are minimal. We view the risks associated with the combined use of nicotine patch and nicotine gum as minimal. Given the now-established safety and validity of nicotine replacement therapies in our prior work and others', we do not view the proposed studies as high risk. In previous studies by our group, standard doses of NRT such as those proposed in this study were extremely well tolerated. Further, nicotine patch and gum are available over-the-counter, also attesting to their excellent safety profiles.

Although we have assessed the proposed study as one of minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study.

Attribution of Adverse Events

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Steven L. Bernstein, MD) according to the following categories:

1. Definite: Adverse event is clearly related to investigational agent.
2. Probable: Adverse event is likely related to investigational agent.
3. Possible: Adverse event may be related to investigational agent.

4. Unlikely: Adverse event is likely not to be related to the investigational agent.
5. Unrelated: Adverse event is clearly not related to investigational agent.

Plan for Grading Adverse Events
The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe unanticipated adverse event resulting inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
4. Life-threatening adverse event
5. Fatal adverse event

Plan for reporting serious AND unanticipated AND related adverse events and anticipated adverse events occurring at a greater frequency than expected to the HIC.
The investigator will report the following types of adverse events to the HIC: a) serious AND unanticipated AND possibly, probably or definitely related events; and b) anticipated adverse events occurring with a greater frequency than expected. These adverse events will be reported to the HIC within 48 hours of it becoming known to the investigator, using Yale HIC Form 6A. Adverse events will be deemed serious in nature if graded as 3 or higher according to the scale in item #4 above.

Plan for Reporting Adverse Events to Co-Investigators
For this study, the following individuals, funding, and/or regulatory agencies will be notified: all co-Investigators listed on the protocol, the HIC, and the National Institutes of Health. The principal investigator (Steven L. Bernstein, MD) will conduct a review of all adverse events upon completion of every study subject. The principal investigator and Dr. Toll will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.
Analytic strategy: overview. Intervention components will be analyzed over three domains, as outlined in Figure 2. First, components will be assessed for clinical efficacy, using traditional measures such as biochemically verified tobacco abstinence. If clinically effective, components will then be analyzed for cost-effectiveness and feasibility/acceptability to providers and subjects. For the economic analysis, we will use standard approaches that assess quality-adjusted life years. For the qualitative assessments, we will interview research subjects to assess the feasibility and acceptability of the intervention components. Components that are clinically efficacious, cost-effective, and feasible and acceptable will be retained in the final package, which will be compared to a control condition in a follow-on randomized clinical trial. Analytic tactics are described in detail in the next few sections.

8. Biostatistical considerations. Primary Study Endpoints and Analyses. The primary efficacy endpoint for this study will be biochemically verified 7-day cessation rate at 3 months.[66] Tobacco use will be assessed by self-report and confirmatory biochemical testing with exhaled carbon monoxide. Patients who assert abstinence by phone interview will be asked to return to hospital for assessment of exhaled carbon monoxide.
Baseline comparability. The adequacy of the randomization will be assessed by comparing the distribution of baseline demographic and clinical characteristics among the intervention groups. Comparability for continuous variables will be examined graphically and by summary statistics,

and categorical variables by calculating frequency distributions. Data analyses will be conducted using SAS 9.3 (SAS Institute, Cary, NC).

Sample size and power calculations. The goal of this proposal is to identify individual tobacco dependence treatment interventions which show clinical efficacy, subject to constraints of cost effectiveness and acceptability. *As each component is allocated to half the participants, the sample size to detect main effects in a full factorial MOST design is not depending on the number of components evaluated, but rather the smallest clinically important difference between the presence and absence of a component*. In our previous trial, we found a difference of 7.3% in biochemically confirmed abstinence between the control and intervention arms at 3 months. It is reasonable to expect that, in this factorial trial, the effect of individual components will be less than that seen in the multicomponent trial.[13,69] Therefore, we have chosen an absolute difference of 5% for the main effects of each component. (We considered a narrower absolute difference of 4%, but the sample size and resources needed become unfeasible.) With a two-sided 0.05 significance level, and an average abstinence proportion of 4.9% in the absence of a component, a total sample size of 860 participants will provide 80% power to detect a 5% increase in the abstinence rate. We will enroll **1056** participants to account for up to a 15% dropout rate by 3 months. *Although we will investigate whether the effect of a component is dependent on the levels of other components (i.e. interactions) our trial has not been powered with the intent to detect these interactions.*

Data monitoring. Procedures for data collection, data management, monitoring of data quality and data analysis have been developed and refined in our previous ED studies. An experienced data manager and Dr. Dziura will supervise this process. Procedures include use of a computerized database system (OnCore) to monitor research activities, screening and enrollment, compliance with protocol and treatment interventions, completion of scheduled assessments, and data retrieval. Data quality will be assured by: 1) extensive training/supervision of RAs in data collection; 2) preliminary review of all assessment instruments prior to data entry and checks for completeness and coding errors; and 3) error-checking statistical programs. No interim looks for efficacy are planned. Monthly reports will monitor accrual, randomization; data timeliness, quality, completeness, and overall event rates (e.g. abstinence). Error corrections will be documented.

Plan for missing data. Several strategies will be used to handle missing data.[70,71] Prevention is the most obvious and effective means to control bias and loss of power. This protocol will follow the intent to treat principle.[72] Telephone visit reminders will be delivered to participants prior to protocol-specified collection times. Alternative contact information will be identified on enrollment to minimize loss to follow-up. Timely data entry combined with weekly missing data reports will trigger protocols for tracking and obtaining missing data items or outcome assessments. We will describe the extent and patterns of missing data and use logistic regression to identify factors associated with non-response. For primary analysis, when data on tobacco abstinence are missing due to attrition or non-response, we will impute relapse to smoking, as is conventional. However, if missing abstinence data are more prevalent in the control group this could lead to a bias in favor of the intervention. While we do not expect differential rates of dropout between groups or high loss to follow-up, sensitivity analysis using pattern-mixture and selection models under missing not at random (MNAR) assumptions will be performed to examine the robustness of conclusions of the primary analysis.[70,73]

Analysis for Aim 1. The primary outcome, abstinence at 3 months, will be compared between the presence and absence of each component using logistic regression. Per convention, in the primary analysis missing abstinence data will be imputed as relapse. For this full-factorial design, the model will include main effects for each of the 4 components as well as all 2, 3 and 4-way interactions. The regression will also include baseline covariates: age, sex, race/ethnicity, and smoking characteristics. Main effects will be evaluated at the 0.05 significance level. Differences in proportions for the presence and absence of each component (i.e. main effects)

will be estimated along with 95% confidence intervals using the bootstrap method.[74] A p-value of 0.10 will be used as a guide to flag potentially important interactions which will be explored graphically with a particular emphasis on identifying substantial synergistic effects or qualitative (i.e. where the impact of one component changes direction depending on the presence or absence of another component) effect modification. Similar analyses will be performed at 1-month follow-up. Additionally, a logistic regression with parameters estimated by weighted Generalized Estimating Equations (GEE) will incorporate both 1 and 3-month outcome data without imputing non-responders as relapse.[75] This analysis weights for the probability of response and is valid under the assumption that missing data are missing at random (MAR). Secondary outcomes at 1 and 3 months will also be evaluated by a generalized linear model with weighted GEE.

9. Economic analysis. Overview. We will perform a series of incremental cost effectiveness analyses (CEA) to determine whether the benefits of each component appear to be worth the added costs, partially accounting for the interactive effects of the components. Two outcomes will be considered: (1) number of abstinent smokers at 3 months (measured by biochemically verified 7-day tobacco abstinence) and (2) the cost per quality-adjusted life year (QALY) saved. Following CEA recommendations,[76,77] baseline analyses will adopt a societal perspective, considering all economic costs regardless of source. We also will calculate incremental cost effectiveness ratios (ICERs) from the payer's perspective, excluding patient costs and, in sensitivity analysis, QL costs. We will use CERs for other cessation interventions to select an acceptable maximum cost/quality-adjusted life year (QALY) saved for the tested program elements since we want to identify an ED cessation approach that is at least as cost-effective as approaches based in other settings.[78-80]
Treatment Costs: We will include costs of all smoking cessation treatment received by participants, broken down by component (Table 3). Resource costs include costs of administering the BNI and medication, texting (a purchased item), and making the QL referral

Table 4. Components of economic analysis.

Component	**Health system cost**	**Subject cost**	**State costs**
Screening	None. Screening information collected for all patients.	None.	None.
Motivational interview	Provider time performing motivational interview (wage X minutes). Average YNHH wage, conditional on provider training (i.e., MD, nurse practitioner, RA) will be used.	None. No additional time in hospital due to motivational interview.	None.
Medication (6 weeks)	Total price paid by hospital. In sensitivity analysis we will consider average wholesale price (AWP), since not all providers receive same medication discounts.	None. Assume all costs of medication borne by provider.	None.
Quitline	None. Provider bears no costs for quit line use.	Cost of time on QL (avg. wage rate X minutes).	Marginal cost of QL user.
Texting	None. Texting will be automated. Once developed marginal cost of texting is small.	Cost of minutes to subject.	None.
Brochure	Printing costs of brochure.	None.	None.

(i.e., IT costs, cost of clinician time to administer the intervention, medication delivered in

hospital, incremental cost of longer follow-up booster phone call), costs related to QL use (i.e., counselor and patient time, cost of written materials, patient time on website), outpatient treatment costs, other medical costs, and patient costs (e.g., time, transportation). In evaluating a prior trial, we measured RA time for an ED-based BNI session. Clinician time costs will include wages, fringe benefits, and overhead. Cost of patient time will be calculated using the average wage rate in the geographic area. Relevant medication use will be obtained from the CPOE record; cost of medication will be based on the average of the current formulary price for the top 5 health insurers in Connecticut. Quitline costs: We will get number of counseling calls completed and costs of written materials used directly from QL records, then calculate costs of counselor and patient time related to the calls (both scheduled QL calls and calls to toll-free number). We will collect patient time on the website at 1 and 3 month assessments. We will exclude research costs because these would not be incurred if our intervention were standard care. Training and texting program setup costs will be excluded from the main analyses. Although these startup costs may be incurred, when distributed across many patients over many years, they would be negligible. We will collect information on training and setup costs and include in publications/sensitivity analysis, as these may be of interest to decision makers.
Measuring Effectiveness. We will assess effectiveness (i.e., abstinence) biochemically at 3 months. With the MOST design, regression will estimate quit rates for the four potential intervention components, as well as the gains and losses that occur when combining them. Over time, abstinence reduces medical care utilization and improves quality of life. We will not track those savings in our patient cohort. Instead, we will update our adaptation of a popular model that simulates them.
Calculating C/E ratios: We will calculate ICERs in two passes. A naive first pass will array cost and regression-adjusted quit rate for each of the 16 MOST cells, ignoring if differences are statistically significant. This naive look will let us drop clearly dominated cells where higher cost is associated with a lower quit rate, as well as any cells that proved infeasible in the clinical setting or were unacceptable to staff. In a refined pass, we will define incremental component cost effectiveness as $\Delta C/\Delta E$, where ΔC is the cost a component adds and ΔE is the effectiveness associated with the component. This refined look at the remaining candidates will use two effectiveness measures, the 3-month quit rate and the simulated quality-adjusted life year (QALY) gain. A QALY is a standard measure of health-related quality of life, defined so that a year in perfect health is valued at 1.0 and death is valued at 0.0.[77] Even if one component costs more per quitter than another, it still may be worthwhile if it helps more smokers to quit at an acceptable cost per QALY gained. By estimating QALYs gained per quitter, we get a measure that lets us judge the cost of cessation gains relative to other smoking interventions, with a tentative ceiling of **$5000** per QALY gained that we will refine in year 4 by updating our literature review on cessation interventions regularly used in medical settings.
The analysis will require estimates of the QALY losses and medical costs averted by smoking cessation. For QALY loss, the most recent estimates[81-83] are better than older estimates.[84,85] For medical costs, we expect to use the latest update to CDC's SAMMEC model[1] which build from the methods pioneered by V. Miller.[86] We will inflate all cost savings to the same year's dollars as the program costs and compute present value of savings in future years at a 3% discount rate. To account for relapse, we will insert our chosen smoking costs and our observed quit rate pattern into the widely used BENESCO (benefits of smoking cessation on outcomes) Markov simulation model of cessation duration or a closely related model.[78,79] These models stem from a 2002 World Health Organization model. The resulting estimates will let us answer the question, which efficacious ED-based interventions maximize quits while staying below the acceptable cost per QALY gained.

To better inform our package choice, we will estimate 95% CIs around the ICERs. To estimate ratio variance, we will start with roughly estimated standard errors or distributional data for each number in the cost-effectiveness equation. We will use bootstrapping simulation

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methods that form an empirical probability distribution.[87] To handle estimates with unknown variance, notably the discount rate, we will conduct sensitivity analyses. The sensitivity analyses examine if different input assumptions would change package selection.

10. *Qualitative analysis*. The final analytic strategy is a mixed methods analysis of those components found to be clinically efficacious. The goal of this analysis is to ensure that those components are considered feasible, practical, and acceptable by the *patients* who we wish to use the package in real-world settings. Intervention components scoring well in Likert assessments and found feasible and acceptable in interviews with subjects (that are also clinically efficacious and cost-effective) will be retained to study in the future randomized trial.

As we did previously, we will conduct phone interviews with study subjects to assess their views of the components, alone and in combination. Unlike our earlier qualitative work, which focused on the texting component only, we will assess subjects' view of all components in the factorial design: texting, BNI, QL, and NRT. *As before*, Likert-type questions will be included. We will make sure to sample individuals who were randomized to each of these as a single intervention. We will also sample individuals who were in arms where we identify important 2-way or 3-way interactions of efficacy.

We will use a grounded theory approach, in which explanatory theories will emerge from inspection of themes derived from coded transcripts.[88,89] All interviews will be audiotaped and professionally transcribed. Interviews will be coded by Dr. Grau and study personnel with experience in coding. Subjects will be interviewed until thematic saturation is reached. We anticipate this will mean 25-30 subjects. Dr. Grau will use ATLAS.ti (ATLAS.ti GmbH).

Telephone interviews will be conducted with subjects during their routine 3-month follow-up phone calls. Consent for the qualitative component will have already been given at study enrollment. We have used this method, with success, in our previous trial of ED-initiated texting. Calls are audiotaped and transcribed by a professional service, with subsequent coding and theming by the study team.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Nicotine replacement therapy—patches and gum—all FDA approved—to be used for treatment of nicotine dependence.

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information: N/A

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?
b. Who holds the IND?
c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____

Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step) Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☐ Yes ☐ No
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☐ Yes ☐ No
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☐ Yes ☐ No
iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☐ Yes ☐ No
v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☐ Yes ☐ No

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):
- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Subjects randomized to NRT will receive 6 weeks of patches (42 count) and gum (300 pieces of 2mg), free of charge. All NRT will be given to the subject in a small shopping bag. NRT dosing is tailored to the patient's score on the Heavy Smoking Index.[47] Patches come in 7, 14 and 21 mg doses. The first patch is applied by an ED nurse during the index visit. This allows us to demonstrate to the subject how to use the patch, its ease of use, and acceptability. It does bypass the traditional model of setting a quit date, although subjects may continue to reduce their tobacco use while using NRT. In our previous study, this approach was accepted enthusiastically by subjects. We employ combination NRT because of its generally greater efficacy than NRT monotherapy in promoting tobacco abstinence.[48]

All smokers will be offered combination treatment with nicotine patch (1/day) and gum (<1 piece/hour), stepped to daily consumption. Smokers with the lightest levels of addiction—<10 cigarettes/day—will be offered a 14 mg patch and 2 mg gum. Subjects may choose only 1 form of NRT, if preferred. Smokers experiencing withdrawal in the ED will be offered gum, irrespective of daily cigarette consumption, because it leads to a relatively rapid rise in serum nicotine levels. The dosing schedule will be determined by the RA in consultation with the patient. Drs. Bernstein and Toll will be available by pager or cell for consultation, as needed.

3. **Source:** a) Identify the source of the drug or biologic to be used.
Nicotine replacement patch – 7 mg, 14 mg, and 21 mg
Nicotine replacement gum – 2 mg

b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
If yes, by whom?
To be purchased by YNHH Pharmacy – Investigational Drug Service using specified grant funding.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
Nicotine patches and gum are ordered by YNHH IDS. A research PYXIS machine was purchased by the department. All NRT is stored in the PYXIS in the YNHH ED.

Check applicable Investigational Drug Service utilized:
☒ **YNHH IDS** ☐ **Yale Cancer Center**

☐ **CMHC Pharmacy** ☐ **West Haven VA**
☐ **PET Center** ☐ **None**
☐ **Other:**

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo:** ☒ **Not applicable to this research project**

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings.*

7. **Continuation of Drug Therapy After Study Closure** ☒ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☐ No If no, explain why this is acceptable.

B. DEVICES – N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
a. targeted for enrollment at Yale for this protocol 1056
b. If this is a multi-site study, give the total number of subjects targeted across all sites N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☐ Flyers ☐ Internet/Web Postings ☐ Radio
☐ Posters ☐ Mass E-mail Solicitation ☐ Telephone
☐ Letter ☐ Departmental/Center Website ☐ Television
☐ Medical Record Review ☐ Departmental/Center Research Boards ☐ Newspaper
☐ Departmental/Center Newsletters ☐ Web-Based Clinical Trial Registries
☐ YCCI Recruitment database ☐ Clinicaltrials.gov Registry (do not send materials to HIC)
☒ Other (describe): RAs will query Epic to determine which patients currently in the YNHH ED are smokers. They will then approach these patients to screen for study eligibility.

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. RAs will query Epic to determine which patients currently in the YNHH ED are smokers. They will then approach these patients to screen for study eligibility.
b. Describe how potential subjects are contacted. RAs will approach patients who are smokers while they are being treated in the ED.
c. Who is recruiting potential subjects? Trained Research Assistants and Research Associates.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☐ Yes ☒ No
b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☐ Names
☐ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
☐ Telephone numbers
☐ Fax numbers
☐ E-mail addresses
☐ Social Security numbers
☐ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers, including license plate numbers
☐ Device identifiers and serial numbers
☐ Web Universal Resource Locators (URLs)
☐ Internet Protocol (IP) address numbers
☐ Biometric identifiers, including finger and voice prints
☐ Full face photographic images and any comparable images
☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☐ Yes, some of the subjects
☒ No

6. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment purposes only

☐ For inclusion of non-English speaking subject if short form is being used

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

We are requesting a HIPAA waiver for recruitment purposes only. The RAs will review the ED Track Board in Epic and will then check the "Smoking Status" for each patient in the ED. They will then approach the patients identified as current smokers or smoking status unknown to ask additional screening questions. We do not have the time and resources to approach every ED patient and ascertain smoking status. Using Epic is more efficient for the RAs.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

☒ Compound Consent and Authorization form

☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

Teresa O'Leary, Kimberly Beauchemin, Elizabeth Jurczak.

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Prospective subjects will be told that we are conducting a study on interventions for health risks and based on their answers to the screening questions they have been identified as eligible for

the study. If patient is interested in hearing about the study, the RA will explain the study. All eligible participants will be asked for written consent using the Yale HIC approved compound authorization form. Consent will be obtained at patient bedside.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

Subjects must be awake, alert, and oriented, and have capacity to consent. Patients mechanically ventilated, clearly delirious or delusional will be excluded. We will not recruit from the CIU, which houses patients with clinically significant and active psychiatric illness.

11. Documentation of Consent/Assent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

An electronic version of the Yale HIC-approved Compound Authorization and Consent Form will be used on a HIPAA-compliant tablet computer. The form is uploaded into the database and the patient is able to review the form on a tablet. The patient signs the form on the tablet with a stylus and the signature is captured in a signature field in the database. For patients uncomfortable with e-consents, paper forms will be provided. An RA will be present throughout the consent process and a copy of the signed form will be printed out for the patient before he/she is discharged from the ED.

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Non-English speaking patients will be excluded as we do not have the ability to provide interventions in languages other than English. Non-English speaking patients will be referred to CT Quitline, as appropriate. If we are fortunate to hire a bilingual RA, e.g. Spanish and English, we will recruit Spanish-speaking patients and use documents translated into Spanish.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?

YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ **Not Requesting a consent waiver**
☐ **Requesting a waiver of signed consent**
☒ **Requesting a full waiver of consent –** for Recruitment/Screening only

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☐ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **Full waiver** of consent: (No consent from subjects will be obtained for the activity.)

☒ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity

☒ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☒ No

c. Why would the research be impracticable to conduct without the waiver?

It is not feasible to consent every ED patient in order to review the patient's smoking status in Epic. We will then ask smokers 3-5 very brief screening questions to determine eligibility. We do not collect PHI on patients we do not enroll in the study.

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? N/A – no PHI is collected on patients we do not enroll in the study.

☐ **Requesting a full waiver of consent for the Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***

☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Name, sex, race, education, employment, health care, insurance, legal issues, behaviors (such as: person safety, tobacco/alcohol/drug use and exercise), patient contact information, contact information of family and/or friends as alternate contacts, primary care providers and specialists will also be recorded to facilitate follow-up.

b. How will the research data be collected, recorded and stored?

Data will be collected using Filemaker for iPad. IPads are encrypted and stored in a locked safe in the RA's locked office in the ED. The iPads are connected to a university-maintained server via an encrypted WiFi connection. This is a live connection; therefore, all data are immediately stored on the secure server. The server is backed up hourly. No ePHI is stored on the iPads. This system is compliant with HIPAA and regulations for the collection of ePHI. Computers are encrypted with PGP software.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.
All paper files with subject information will remain in locked files in the study office of the PI. At the end of data collection, any identifiable data/PHI will be removed from the database. After this is done, only de-identified data will be maintained in a password-protected file on a password-protected network server to which only the PI, co-investigators and study personnel will have access. After publication, all remaining paper and electronic data will be destroyed.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)
Only the study team listed on the protocol will have access to PHI and the study database.

If a subject is randomized to one of the 8 arms with the texting component, we will receive information about the subject's utilization of the texting program from ICF International, vendor for SmokefreeTxt. A Data Use Agreement has been executed specifying that ICF will send us unmasked reports of utilization (did subject opt out, subject's responses to Ecological Momentary Assessment (EMA) questions, etc). We will be able to link ICF's records back to the study subjects using subjects' cell phone numbers. No other PHI will be exchanged between ICF and Yale.

g. If appropriate, has a Certificate of Confidentiality been obtained? Yes

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.
N/A

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
Subjects will receive a medical evaluation at no charge. In addition, subjects will receive potentially beneficial treatment for nicotine dependence free of charge. The medical counseling, quitline referral and nicotine replacement therapy that participants may receive are standard treatments that have been shown to be efficacious for smoking cessation. Mobile phone texting, a newer modality, shows promise as well.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   The alternative to study participation is to not participate. If a patient expresses interest in smoking cessation but does not want to participate, the RA can give the patient a brochure for the CT Tobacco Quitline, a free service available to any resident of CT. The Quitline offers counseling and cessation medications.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   All subjects are eligible to receive up to $50 for enrollment and completion of 2 follow-up phone calls. All subjects will receive a $10 gift card at enrollment, a $20 gift card for completion of the 1 month follow-up and a $20 gift card for completion of the 3 month follow-up. Subjects randomized to the texting arm will receive an additional $20 gift card to cover the cost of minutes on their phone plans. For subjects reporting tobacco abstinence at 3 months, an additional $200 is offered for returning to the hospital to measure exhaled breath carbon monoxide. For subjects asked to complete the qualitative interviews, a $40 gift card will be offered.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   Patients randomized to the texting arm who do not have unlimited texting on their cell phone plans may incur messaging charges associated with study enrollment. We intend to give subjects in the texting arm an additional $20 gift card at enrollment to offset this potential cost.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs? Yes.
   b. Where and from whom may treatment be obtained? Routine sources of care.
   c. Are there any limits to the treatment being provided? Not anticipated.
   d. Who will pay for this treatment? None anticipated this is largely minimal risk.
   e. How will the medical treatment be accessed by subjects? Via PCP or YNHH. Can be referred for treatment by PI, if needed.

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