Detailed Protocol

TITLE: Smoking interventions for hospital patients: A comparative effectiveness trial
PI: Nancy Rigotti
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BACKGROUND AND SIGNIFICANCE:

Tobacco use is the leading cause of preventable death in the United States. Tobacco use is the United States’ leading cause of preventable death, accounting for 435,000 deaths per year (Mokdad 2004). Cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and lung cancer are the main causes of tobacco-related mortality. In 2007, 19.8% of U.S. adults smoked cigarettes (CDC, 2008). A Healthy People 2010 objective is to reduce adult smoking prevalence to less than 12%.

Smoking cessation prevents disease, improves health, and is highly cost-effective.

Smoking cessation has health benefits for men and women of all ages, even those who do not stop smoking until they have developed cardiovascular or pulmonary disease (Fiore 2008). Smokers who quit smoking after a myocardial infarction (MI) reduce subsequent all-cause mortality by 36% (Critchley 2003). Smoking cessation in this setting is highly cost-effective and is a cornerstone of secondary CVD prevention efforts. Smokers with COPD who stop smoking also reduce subsequent mortality rates (Anthonisen 2005). Smoking cessation is recommended by clinical guidelines for secondary prevention of CVD and for treatment of COPD.

Effective smoking cessation treatment exists but does not reach most smokers.

The 2008 U.S. Public Health Service (USPHS) Treating Tobacco Use and Dependence clinical guideline identified effective treatments and made recommendations for actions to be taken by clinicians, hospitals, and health care systems (Fiore 2008). Effective treatments include (1) smoking cessation counseling (delivered in person or by telephone) and (2) pharmacotherapy with nicotine replacement (NRT), bupropion, or varenicline. Counseling and medications are each effective alone, but combining the two is more effective and is recommended by the guideline, which outlines a 5-step algorithm, commonly called the “5As” – Ask, Advise, Assess, Assist, Arrange – to translate effective tobacco treatment methods into actions that clinicians and hospitals can take (Fiore 2008). Unfortunately, only 25% of smokers who try to quit smoking use these proven treatments, and the long-term abstinence rate from unaided quit attempts is only 5% (Shiffman 2008). To improve quit rates at the population level, we could improve the efficacy of interventions but we could also simply increase the impact of existing treatment by extending its reach—e.g., the proportion of smokers who use it.

A hospital stay provides a special opportunity to encourage and assist with smoking cessation.
The health care system is an important channel for delivering tobacco treatment to the population. Each year, nearly 4 million smokers (8.7% of all smokers) spend at least one night in a hospital. This event provides a “window of opportunity” to initiate smoking cessation. First, smokers must temporarily abstain from tobacco use in the hospital because US hospitals are now smoke-free. Smokers have an opportunity to try out abstinence in an environment devoid of usual environmental cues to smoke. Second, illness, especially if tobacco-related, boosts receptivity to smoking cessation messages by increasing perceived vulnerability, a so called “teachable moment.” Third, illness brings smokers to the health care setting, where they have contact with health professionals who can provide smoking cessation assistance. For these reasons, providing (or at least initiating) smoking cessation treatment in hospitals is potentially a cost-effective preventive health strategy and an effective strategy to extend the reach of tobacco treatment to smokers at a population level.

Smoking cessation interventions that begin in the hospital are efficacious in research settings but must continue contact after hospital discharge to produce long-term tobacco abstinence.

Counseling
Randomized controlled trials published since 1990 have demonstrated the efficacy of hospital-based smoking counseling interventions (Taylor 1990). Thirty-three trials were reviewed in a 2008 Cochrane collaboration meta-analysis, done by the PI (Rigotti 2008). This systematic review established the efficacy of hospital initiated smoking counseling intervention. Smoking cessation counseling that began during a hospital stay increased the odds of tobacco abstinence at 6-12 month follow-up by 65% (OR 1.65, 95% CI 1.44-1.90) but only if it included sustained (>1 month) telephone support after discharge. The intervention was effective regardless of the reason for admission, but was not effective with a shorter duration of support after discharge. The review concluded that smoking counseling interventions should be offered to hospitalized smokers regardless of admitting diagnosis.

Pharmacotherapy
Although counseling interventions have been tested in many studies, the efficacy of pharmacotherapy by itself, without any behavioral support, has not been tested in hospitalized smokers (Rigotti 2008).

Combinations of counseling and pharmacotherapy
The 2008 USPHS clinical guideline finds that counseling and pharmacotherapy each significantly and independently increase the odds of smoking cessation (OR, 1.3 to 3.6) in the outpatient setting. Furthermore, they are synergistic; each adds benefit to the other when they are combined (Fiore 2008). In the hospital setting, the marginal benefit of adding pharmacotherapy to counseling (or vice versa) has received little attention. Six studies have tested the additional benefit to be gained by starting smoking cessation pharmacotherapy in the hospital and continuing it after discharge. In 5 of these studies, adding nicotine replacement therapy (NRT) to counseling produced an increase in the odds of long-term cessation (pooled OR 1.47) but it was not statistically significant (95% CI 0.92-2.35)(Rigotti 2008). Bupropion was tested in only one trial, done by the PI, that
had a similar nonsignificant effect (OR 1.56, 95% CI 0.79-3.06) (Rigotti 2006).

Varenicline has not been tested in the hospital setting. The evidence, though not conclusive, was deemed sufficient to support a tentative recommendation to add pharmacotherapy to counseling to promote long-term cessation after hospital discharge (Rigotti 2008). The review called for additional evidence to strengthen this evidence base. It also noted that NRT had another indication for use in hospitalized smokers: to reduce the discomfort of nicotine withdrawal during temporary tobacco abstinence.

Only one study has tested the marginal benefit of adding behavioral support to pharmacotherapy started in the hospital. Proactive telephone counseling after discharge increased the smoking cessation rate at 1 year follow-up, from 7% to 14%, among smokers who were provided a course of NRT (Simon 2003). This is consistent with a body of evidence that cognitive-behavioral counseling by itself may provide practical relapse prevention skills and increases smokers’ self-efficacy (confidence in their ability) to stay quit (Hajek 2005). However, telephone contact with a counselor might have the additional independent effect of providing medication management to help manage any adverse effects of pharmacotherapy and promote medication adherence. This has not been directly tested for smoking cessation medications but is consistent with evidence-based strategies to optimize medication adherence for other diseases.

**Unfortunately, truly evidence-based hospital smoking interventions are not widely implemented.**

Although hospital based smoking cessation is effective, evidence-based hospital smoking interventions that include sustained contact after discharge are not widely adopted in current practice. The provision of smoking advice and counseling to hospitalized smokers has increased since 2004, when a tobacco treatment measure was added to the publicly-reported National Hospital Quality Measures (NHQM) set by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and Medicare. The tobacco measure reports on the proportion of smokers who received smoking advice, counseling, or medication during a hospitalization for acute myocardial infarction, congestive heart failure, or pneumonia. However, the measure does not require hospitals to link patients to continued tobacco intervention after hospital discharge. According to the findings of the Cochrane meta-analysis, programs that only meet the NHQM standard and do not connect to sustained support after hospital discharge are unlikely to improve long-term smoking cessation rates.

**The result is a missed opportunity to impact population smoking rates by translating research into practice.** An evidence-based, cost-effective intervention model that is feasible to disseminate widely to U.S. hospitals is needed in order to realize the potential impact of interventions for hospitalized smokers. This was one of the conclusions of a NIH-sponsored Working Group on Smoking Cessation in Hospitalized Patients that was held in September 2008 and was co-chaired by the PI. The 2008 meta-analysis of hospital smoking interventions identified the most pressing research need as identifying models to translate efficacious interventions from research settings into routine practice in hospitals and demonstrating the effectiveness of these models (Rigotti 2008). Assessing the cost-effectiveness of practical intervention models,
clarifying the marginal efficacy of adding pharmacotherapy to counseling, and assessing the impact of hospital interventions on health care utilization (hospital readmissions) or clinical outcomes were other knowledge gaps identified.

Summary and Potential Impact

The 2008 U.S. Public Health Service Smoking Cessation Guideline recommends offering treatment, which includes counseling and pharmacotherapy, to all smokers in every health care setting. A hospital admission provides an opportunity for a smoker to quit. A strong base of evidence consisting of randomized controlled trials conducted in research settings supports the efficacy of smoking interventions for hospitalized patients. These show that smoking cessation counseling interventions provided in the hospital are effective, but only if they include contact, usually by telephone, that lasts for >1 month after discharge. Smoking cessation medications appear to add benefit to hospital-based counseling if they are continued after discharge. However, this evidence-based smoking intervention has not been translated into practice. The result is a missed opportunity to impact smoking cessation rates for the nearly 4 million smokers who are hospitalized each year. To address this challenge, this project aims to overcome the barriers that are hindering the translation of this research into routine clinical practice.

The Approach

Our goal is to develop an innovative, cost-effective strategy to take advantage of the opportunity to change smoking behavior that a hospital admission provides. We aim to increase long-term smoking cessation rates among hospitalized smokers by translating strategies proved efficacious in research settings into a practical cost-effective model that can be readily implemented by U.S. hospitals. This project will develop and test a new model of care (Extended Care) that incorporates and builds on intervention proved efficacious in research settings. It will be compared to a Standard Care model that is currently in practice at the study site, meets current National Hospital Quality Standards, and reflects optimal current practice. The Extended Care model adds to the Standard Care model a post-discharge intervention package that is intended to encourage and facilitate smokers’ use of continued tobacco treatment (both counseling and pharmacotherapy) after discharge. It includes 3 innovations. These innovations are designed to solve barriers to the translation of research into practice:

1. a free 30-day supply of smoking cessation medication at hospital discharge with the option to renew twice for 90 days of free medication total.
2. a series of proactive telephone counseling calls for 3 months after discharge that aim to promote adherence to smoking cessation medication in addition to providing the psychosocial relapse prevention support that was provided in past research studies.
3. the use of Interactive voice recognition (IVR) technology to make counseling more cost-effective.

Our theoretical framework is that tobacco use is a chronic disease requiring long-term management. Chronic disease management strategies developed and implemented for other chronic disease such as CVD and asthma need to be applied to tobacco treatment (Sherman 2008, Steinberg 2008, Fiore 2008). Our approach is influenced by
the theoretical structures of the Chronic Care Model (Wagner 1996), which identifies the
types of interventions needed to manage chronic diseases, the RE-AIM Framework
(Reach, Effectiveness, Adoption, Implementation, Maintenance), which provides a
conceptual model for assessment (Glasgow 2001), and consumer product design
principles adapted to stimulate demand for tobacco treatment (NTCC 2008). It is
designed to overcome barriers to translation.

Barriers to translating research into routine practice

Hospital discharge is a high-risk situation. The addictiveness of nicotine
makes relapse to smoking a risk after any quit attempt. When the quit attempt is
triggered by a hospital admission, hospital discharge is especially risky. First, nicotine
withdrawal symptoms, which peak at 3 days after tobacco abstinence begins and last
for several weeks, are still present at discharge. Second, the smoker returns to an
environment filled with his/her usual cues to smoke. These trigger cigarette cravings
and add to the relapse risk. Prior work by the PI indicates that at least half of smokers
resume smoking by 3 days after hospital discharge (Rigotti 1996).

Interventions used in research studies do not fit neatly into the health care
delivery system. The intervention model found to be effective in research studies does
not fit easily into the existing health care delivery system. Implementing the model
requires coordinating care from the inpatient to the outpatient setting. Bridging this gap
is a major challenge for the management of all chronic diseases, and tobacco treatment
is no exception. Hospitals do not see post-discharge care as their responsibility in
general and are not eager to bear the cost. For tobacco use specifically, opportunities
for reimbursement are limited by the fact that tobacco dependence treatment is not well
covered by health insurers, who are not eager to add new
benefits in an era of soaring health care costs, even if the therapies are cost-effective.

Potential Solutions

Avoid gaps in care. A plan to prevent relapse after discharge must be in place
and ready to implement as smokers leave the hospital. Gaps in providing this care could
produce early relapse to smoking.

Reduce barriers to medication use. Previous research focuses primarily on
providing counseling after discharge. Pharmacotherapy deserves a greater emphasis,
as noted in the recent meta-analysis of hospital interventions (Rigotti 2008). Consumer
demand design principles (NTCC 2008) have been applied to stimulating demand for
tobacco treatment. These principles stimulated us to use these strategies: (1) offer a
free starter supply of the patient’s choice of medication and have it in the patient’s
possession at hospital discharge in order to address the barriers of cost and
convenience. (2) Add medication management as an additional component of the post-
discharge telephone calls.

Broaden the goals of counseling. Tobacco cessation counseling traditionally
focuses on increasing motivation to quit, teaching cognitive-behavioral skills to avoid
relapse, and increasing self-efficacy (self-confidence in the ability to stay quit). We
broadened the focus and applied these strategies to improve patients’ adherence to
effective medications and the likelihood of completing a full course of treatment. We
hypothesize that improving adherence will increase the effectiveness in actual practice
of smoking cessation pharmacotherapy. This is a standard chronic disease management approach.

*Increase the cost-effectiveness counseling with a novel technology.* As described below, interactive voice recognition (IVR) technology can automate the process of making repeated proactive postdischarge calls and limit counselor time to the smokers most likely to benefit.

**Innovations**

**Offering a free sample of medication at discharge.** The Extended Care model will promote medication use by offering a free 30-day supply of smoking cessation medication at hospital discharge (that can be renewed twice after hospitalization) and ensuring that medication is in the smoker's possession as the smoker leaves the hospital. We are adapting a successful public health strategy to the health care setting. Telephone quitlines in many states have offered free samples of nicotine replacement to the public. Multiple studies have demonstrated that this strategy increases smokers' demand for and use of smoking cessation treatment and increases smoking cessation rates compared to historical controls (Miller 2005, An 2006, Fellows 2007, Tinkleman 2007). By increasing both efficacy and reach of treatment, it has increased the population impact of treatment. This strategy has not been tested to promote smoking cessation in hospital settings. Pilot data from the MGH Tobacco Treatment Service shows that smokers who use nicotine replacement (NRT) after hospital discharge have higher short-term tobacco abstinence cessation rates (OR 1.40, 95%CI: 1.24-1.60). The effect did not persist long-term because few patients used NRT for more than 2 weeks. One reason is that NRT is nonprescription and rarely covered by insurance. Providing a free 1-month supply of NRT or any FDA-approved smoking cessation medication is hypothesized to increase smokers' use of medication after discharge and their long-term cessation success.

**Interactive voice recognition (IVR) technology** is used make counseling more cost-effective. IVR is a telephone technology in which a computer detects voice and touch tones and responds to callers with prerecorded audio. A “call-out” IVR system, in which a computer initiates the call, has the potential to improve that cost-effectiveness of outcome assessment by substituting a computer for a human caller. IVR systems can improve response rates by making multiple calls and doing so outside normal business hours. IVR has the capacity to reach smokers to provide support during the critical early post-discharge period and to provide contact often and at a time convenient for the patient. This might reduce relapse to smoking after discharge. IVR systems have been used in medical settings to assess patients for adverse outcomes after outpatient surgery (Piette 2000, Abu 2007, Forster 2009, Reidel 2008). Colleagues at the Ottawa Heart Institute have adapted IVR technology for providing telephone counseling to smokers after hospital admission for coronary heart disease. Their uncontrolled study demonstrated the feasibility and promise of IVR technology (Reid 2006).

**Preliminary work**

To gain experience with the IVR system, we adapted the IVR system developed in Ottawa to all hospitalized smokers and to the U.S. setting. We conducted a randomized
trial of 2 levels of IVR follow-up after hospital discharge from December 2007 through July 2008 among 731 smokers hospitalized at MGH. We compared these groups to 691 historical controls referred to the TTS from April through September 2007. Historical controls (Pre-IVR) had post-discharge outcomes assessed with live telephone calls at 2 and 12 weeks after discharge. The IVR group had the 2-week assessment initially made by an IVR call, with human telephone calls made if IVR calls failed. The IVR + Call Back (IVR+CB) group received a series of 4 IVR calls (at 3, 7, 14, and 30 days) after hospital discharge. These calls assessed smoking status and also offered to have a tobacco counselor contact the patient. IVR participants who had not smoked in the past 7 days or wanted to quit within the next 2 weeks were eligible for a call back from the hospital smoking counselor. Counselors attempted to reach those requesting call backs within 48 hours and reached over 80% of them. Response rates with IVR were 73% and 62% at 2-week and 12-week follow-ups, respectively, and were comparable to the historical control group (71% and 63%, respectively). At 2 weeks, the self-reported quit rate, assuming that patients lost to follow up were smoking, was 38% in the IVR group, 39% in the IVR+CB group and 28% in the historical controls. At 12 weeks, quit rates were 27% in the IVR group, 29% in the IVR+CB group, and 22% in historical controls. This pilot work established the feasibility and acceptability to patients of IVR in our setting. IVR produced slightly higher quit rates than historical controls after adjustment for confounders, but the call back option did not add to IVR alone. We propose to strengthen the call-back intervention in this proposed trial by (1) adding more IVR calls, and (2) expanding eligibility for call backs to include noncompliance to pharmacotherapy.

Potential Impact: Nearly 4 million U.S. smokers are hospitalized each year. Many of them are at high risk for tobacco-related mortality due to CVD, COPD and other diseases. This project could identify a strategy to translate an efficacious smoking intervention from research into routine hospital practice, thereby increasing the reach and impact of tobacco treatment at the population level. It could also provide evidence to support an improved NHQM hospital quality measure. Over the past 4 years, Massachusetts General Hospital, under the sponsorship of its Quality Improvement Program and the leadership of the Principal Investigator, has implemented the innovative NHQM-compliant Standard Care model and has pilot tested components of the Extended Care model. The infrastructure and administrative supports are already in place to ensure that the project can be completed in the Challenge Grant’s time frame.

SPECIFIC AIMS
Specific Aim: To conduct a randomized controlled comparative effectiveness trial of two strategies to promote smoking cessation in hospitalized patients: (1) a hospital-only intervention that meets NHQM/JCAHO hospital quality standards (“Standard Care”), and (2) an “Extended Care” model that aims to facilitate smokers’ sustained use of smoking counseling and medication after hospital discharge in order to produce long-term abstinence. It will provide 3 months of telephone contact after hospital discharge and feature 2 innovations. First, to increase medication use, smokers willing to make a quit attempt will receive a free 30-day sample (with the option to renew 2 times for 90
days of medication total) of their choice of FDA-approved smoking cessation medication (nicotine replacement, bupropion, or varenicline) at hospital discharge. Second, to improve counseling cost-effectiveness, interactive voice recognition (IVR) technology will be used to make automated telephone calls after discharge in order to identify the subset of smokers most likely to benefit from continued counseling that will be provided by a central telephone smoking counselor. This should improve the cost-effectiveness of the counseling intervention. The counselor will provide both counseling and support for medication management and adherence. The proposed randomized controlled trial will enroll 330 adult smokers admitted to Massachusetts General Hospital, a 900-bed teaching hospital in Boston, MA. Outcomes will be measured 1 and 6 months after hospital discharge by patient survey. Cost-effectiveness analysis will compare the interventions’ on their cost per smoker quit.

Hypotheses: Extended Care, as compared to Standard Care, will:

- Be feasible to implement in actual hospital practice
- Increase the proportion of hospitalized smokers who use evidence-based tobacco treatment (either smoking counseling or medication) after hospital discharge
- Increase the duration of tobacco abstinence after hospital discharge
- Increase the rate of tobacco abstinence at 1 and 6 month follow-up after hospital discharge. The primary outcome is 7-day point-prevalence tobacco abstinence, verified by saliva cotinine or proxy corroboration of nonsmoking, at 6 month follow-up.

SUBJECT SELECTION:

Subjects will be male and female adults (age >18 years) who are admitted to MGH, are current smokers (defined as smoking at least 1 cigarette in the week before hospital admission), agree to try to quit smoking after hospital discharge, live in southern New England, and have an expected hospital stay of >24 hours are eligible for the study. Exclusion criteria include the following: no access to a telephone; active substance abuse (other than tobacco) in the past 12 months; unable to give informed consent or participate in counseling due to serious psychiatric disorder (e.g., schizophrenia, psychosis) or severe cognitive disorder (e.g., dementia, severe mental retardation); life expectancy <12 months or medical instability that would preclude study participation.

SUBJECT ENROLLMENT:

Recruitment and Enrollment Subjects will be recruited as part of MGH’s standard treatment protocol for inpatients who smoke; this is described below under “Standard Care.” Patients admitted to MGH routinely have their smoking status assessed at admission by the admitting physician using the hospital’s computerized order entry system, which automatically refers all smokers to the MGH Tobacco Treatment Service (TTS). A TTS counselor sees all admitted smokers, usually on the second hospital day. During the study period, TTS counselors will flag eligible patients and will introduce the study to these patients. If a patient is interested in the study, the TTS counselor will contact the study research
assistant who will describe the study in detail, obtain written informed consent, and enroll the subject. Following baseline data collection at the bedside, the research assistant will assign the subject to a treatment group and initiate the extended care intervention for the appropriate subjects.

Baseline data collection will include demographic factors, admitting diagnosis, admitting service, smoking and quitting history, measures of nicotine dependence (cigarettes smoked/day in month before admission and time to first morning cigarette), intention to remain abstinent from tobacco after hospital discharge, and detailed contact information for the patient and 3 close contacts. Some of the data is routinely collected by the TTS counselor and entered into the TTS electronic database. It will be supplemented by additional data collected by the study research assistant.

Assignment to Study Arm
Subjects will be randomly assigned to treatment condition (standard care vs extended care) in a 1:1 fashion in blocks of 8. Randomization will be stratified by primary admitting diagnosis (cardiac vs other) because smokers admitted with TTS data show that this is a major predictor of post-discharge abstinence. Stratification will ensure that the treatment groups are balanced on this potential confounder. The study biostatistician will develop a computer generated randomization scheme for each stratum.

STUDY PROCEDURES:
All participants will be seen by the TTS while in the hospital per hospital protocol. Those interested in the study will have an enrollment visit with the study research assistant while in the hospital. In addition, all participants will receive a follow-up phone call to assess for smoking status and medication use at 1 month and 3 months post-quit. Participants in the Extended Care condition will also receive up to 5 calls from our Interactive Voice Recognition (IVR) system and the offer to receive 5 telephone counseling sessions with TTS counselors. These calls will take place at 3 days and 2, 4, 8, and 12 weeks after discharge. The IVR calls are made by TelAsk, the IVR vendor.

Interventions
Standard Care
All subjects in the trial will receive all components of the Standard Care intervention arm. MGH has an ongoing internally-funded Tobacco Treatment Service (TTS), directed by Dr. Rigotti (PI). The TTS is responsible for providing a smoking intervention to all admitted smokers. Its protocol is designed to comply fully with the National Hospital Quality Measures. It includes the following as standard care:

(1) Bedside pamphlet: “A Guide for Hospital Patients who Smoke” pamphlet is part of the standard MGH admission packet that is left at the bedside for all new admissions regardless of smoking status. The 4-page pamphlet provides advice to quit, information about managing nicotine withdrawal symptoms and craving in the hospital, and contact information for hospital and community smoking cessation resources that can be contacted after discharge for assistance.
Routine smoking status identification: Patients' smoking status is routinely identified in an electronic database at admission. Smoking status is included on the MGH computerized order entry system's admitting template which admitting physicians complete to admit a patient. The MGH TTS receives a daily electronic download of all admitted smokers.

Bedside smoking counseling: Newly admitted smokers are seen by 1 of 3 TTS counselors during weekdays. TTS counselors are specially trained nurses or social workers who are Certified Tobacco Treatment Specialists. Counselors use a standard protocol to manage nicotine withdrawal symptoms, provide smoking cessation counseling, and make medication recommendations. For continued support after discharge, counselors provide contact information for MGH outpatient smoking cessation programs and Massachusetts Smokers Helpline (state telephone quitline). Median contact time for counseling visit is 20 minutes. Counselors record standard data on each patient with a data collection form that is entered into the TTS program electronic database.

Pharmacotherapy: Nicotine replacement therapy (NRT) (patch, gum, lozenge, and inhaler), bupropion, and varenicline can be prescribed to inpatients through the hospital formulary. According to TTS records, 33% of patients admitted in 2007 were prescribed NRT in hospital.

Extended Care
The Extended Care model includes all components of Standard Care but adds a post-discharge intervention package that is intended to encourage and facilitate smokers' use of continued tobacco treatment (counseling and pharmacotherapy) after discharge. This begins at the end of the hospital stay and continues for 3 months after discharge. The Extended Care model offers a free supply of smoking cessation medication at hospital discharge and a series of proactive telephone counseling calls for 3 months after discharge. Interactive voice recognition (IVR) technology is used make counseling more cost-effective. Extended care includes two intervention components beyond standard care and incorporates novel strategies.

Smoking cessation medication: Smokers willing to make a quit attempt will be given a free 30-day supply of the FDA-approved smoking cessation medication (nicotine replacement, bupropion, or varenicline) of their choice at the end of the hospital stay (with the option to renew the medication twice for up to 90 days of free medication). The TTS counselors routinely make medication recommendations to all patients that include recommendations for medications to use after hospital discharge. Recommendations reflect the patients' medical history, prior quitting experience and experience with smoking cessation medications, and patient preference. This information is included in a note in the patient’s hospital chart and will also be communicated directly from the TTS counselor to the study research assistant. The research assistant will contact the attending physician to obtain approval and a formal medication order. Upon approval from the doctor, the research assistant will then obtain a 30 day supply of the medication from outpatient pharmacy and deliver it to the patient’s nurse, who will give it to the patient as part of the discharge instruction process and make sure that it is listed on the patient’s discharge medication list. The medication package will include written information on proper medication use and side effects to watch for, along with instructions to contact the patient’s primary care physician and/or the MGH TTS in case
of problems. Patients will be given the option to renew their medications for up to 3 months total of free medication treatment through the automated telephone system.

(2) Sustained counseling support by telephone for 3 months after hospital discharge: Patients in this arm will be contacted by telephone 5 times in the 3 months after discharge to provide this level of care. Two innovations are proposed to improve the cost-effectiveness of the intervention.

First, interactive voice recognition (IVR) technology will be used to make the initial automated proactive telephone calls at each follow-up point after discharge in order to identify the subset of smokers most likely to benefit from counselor contact. The study research assistant will transfer information about the patient’s name, phone number and their date of discharge to IVR vendor (TelAsk) via a secure, password protected server. The IVR system will make 5 outbound calls at 3 days and 2, 4, 8, and 12 weeks after discharge. Each call will assess: (1) patient’s current smoking status, (2) whether the patient is using smoking cessation pharmacotherapy, and (3) patient’s desire to receive a call back from a hospital smoking counselor. The IVR system will put information about any patient who desires a call back into a secure web-accessible database that the study coordinator and TTS counselors will monitor daily. Within 48 hours, a TTS counselor, ideally the one who saw the patient in the hospital, will make up to 3 attempts to reach the patient at the patient’s preferred time and number. In our pilot work, 25% of patients who were reached by IVR requested a counselor call-back. Counselors were able to reach 80% of patients with little difficulty.

Second, the content of the follow-up telephone counseling will expand to include medication management and adherence support. Previous studies have focused on providing cognitive-behavioral counseling support for relapse prevention (Taylor 1990, Rigotti 2008) and found this to be useful. Counselors in this trial will provide this but also provide counseling focused on medication management and which aims to maintain the smoker’s adherence to the free sample of medication and to complete a full course of medication by obtaining additional medication from our study after 1 month.

BIOSTATISTICAL ANALYSIS:

Assessment Plan

This project aims to demonstrate that the Extended Care model can be implemented and assess its effect on study outcome measures. The assessment will test the study hypotheses: Compared to Standard Care, the Extended Care model will:

- Increase the proportion of hospitalized smokers who use evidence-based tobacco treatment (either smoking counseling or medication) after hospital discharge
- Increase the duration of tobacco abstinence after hospital discharge
- Increase the rates of tobacco abstinence at 1 and at 6 month follow-ups after hospital discharge
- Be feasible to implement in actual hospital practice
Outcome Measures

1o Outcome Measure: Verified 7-day point prevalence tobacco abstinence at 6 month follow-up

2o Outcome Measures:
Self-reported 7-day point prevalence tobacco abstinence at 1 month, at 6 months
Sustained tobacco abstinence (= abstinence at both 1 and 6 months)

The primary outcome is 7-day point-prevalence tobacco abstinence, verified by saliva cotinine or proxy corroboration of nonsmoking, at 6 month follow-up. This is a widely-accepted measure of long-term smoking cessation for research trials. We will use a standard measure, 7-day point prevalence abstinence, based on this question: “Have you smoked a cigarette, even a puff, in the past 7 days?” The rate of relapse after a quit attempt is rapid in the first 3 months and then reaches an asymptote. Six-month follow-up is a widely-accepted minimum for assessing long-term abstinence in clinical trials and in Cochrane Collaboration meta-analyses.

Standard practice also requires verification of patients’ self-reported tobacco abstinence in smoking cessation clinical trials. Subjects who self-report 7-day abstinence will be asked to provide a saliva sample for biochemical verification using cotinine, the major nicotine metabolite that can be measured in saliva, serum, or urine and reflects nicotine exposure in the prior 4-5 days. Use of nicotine replacement provides a false positive result. For such patients, we will request a study visit to obtain a measure of expired-air carbon monoxide, another standard verification method. Saliva samples have been obtained by mail by our group and others. This data collection method produces valid results. Samples will be frozen and sent to a laboratory that conducts these assays for research projects. Smokers will be offered a $50 for returning the sample or doing the CO validation visit. We have used this protocol successfully in past clinical trials in health care settings. As a back-up strategy for self-reported smokers who are unable to provide a saliva sample – or those who are using nicotine replacement therapy or who cannot make a visit for a CO measurement – we will obtain proxy validation from a spouse, close relative or close friend. Patients who self-report nonsmoking but do not provide a saliva sample or CO measurement or proxy corroboration or whose saliva cotinine exceeds >10 ng/ml or expired air CO >8 ppm will be considered as smokers for analysis. Subjects who are lost to follow-up are counted as smokers, as is standard practice.

Additional outcome measures to be measured are self-reported abstinence at 1 month, self-reported abstinence at 6 months, and a measure of sustained abstinence, defined as abstinence reported at both 1 and 6 months and verified at 6 months.

2o Outcome Measure: Use of tobacco treatment (any smoking cessation medication or counseling) in past 6 months

Use of treatment is an intermediate outcome, since we hypothesize that the intervention works by increasing the proportion of subjects who use treatment after hospital discharge. The measure of treatment use is a composite because each component has been shown to significantly and independently increase the odds of smoking cessation (OR, 1.3 to 3.6). The components are:

Smoking cessation counseling = contact with a TTS counselor, telephone counseling by the Massachusetts Smokers Helpline or in-person counseling from a local
hospital program or other source. This will not include non-evidence-based interventions such as acupuncture or hypnosis.

   Smoking cessation pharmacotherapy = use of NRT (nicotine patch, gum, lozenge, inhaler, or nasal spray), bupropion, or varenicline. Analyses will also explore the effect of the two interventions on individual components of this measure (e.g., pharmacotherapy use, counseling use). Initial analyses will use the measure of any use of treatment after discharge.

   Additional analyses will assess the proportion of subjects who use treatment components for >1 month, since that is the criterion of post-discharge support duration identified by the 2008 meta-analysis.

2o Outcome Measure: Duration of tobacco abstinence after hospital discharge

   This is an intermediate outcome that will be assessed by self report at 1 and 6 month follow-up points. Subjects will be asked how many days passed before they smoked any cigarette. An alternative measure is to assess whether a smoker made a quit attempt (defined as >24 hours of intentional abstinence), but this is difficult to answer for a patient who has just left the enforced abstinence of a hospital. Duration of abstinence, as a continuous variable, also permits a more nuanced assessment of relapse prevention.

Feasibility

   We will assess the overall feasibility of the Extended care model and the feasibility of individual components as follows.

      Overall feasibility: % of eligible subjects who enroll, % who complete study
      Feasibility of IVR: % of subjects in Extended Care condition who accept any IVR call, % who accept each specific call, mean number of calls accepted
      Feasibility of free medication offer: % of those eligible for medication who accepted the offer and % who used any of the free medication
      Feasibility of counselor callbacks: % of subjects who request a call back, % of those requesting a call back who were reached within 5 days

Outcome Assessment:

   Patient survey: Outcomes will be assessed 1 and 6 months after hospital discharge. Outcome assessments will be conducted by telephone by a research assistant unaware of the patient's group assignment and distinct from the research coordinator or TTS counselors. Up to 6 calls will be made at different times of day and days of the week in order to maximize response rate. In our evaluations of Standard Care and in the pilot trial of IVR, we were able to contact 75% of subjects at 2 week follow-up and 63% at 12 week follow-up.

   Other data sources for outcome assessment will include records of the MGH TTS program and a research study database that will be set up for this project.

Statistical Analysis

   We will use an “intention to treat” analysis strategy. Cross-sectional analyses will be conducted for outcomes assessed at 1 and 6 months after discharge. Chi-square tests will be used to compare smoking cessation rates and treatment use between the
Extended Care group and the Standard Care group at each time point. Logistic regression analysis will be used to compare the two groups controlling for other factors. A longitudinal analysis using Generalized Estimating Equations (GEE) techniques will be used to assess the overall impact including data from all follow-up times. All patients with missing smoking status outcomes will be considered as smokers at that follow-up point. Patients who report tobacco abstinence at 6 months but do not verify the outcome with either a saliva cotinine < 10 ng/ml, CO<9 ppm or proxy verification will be considered smokers for the primary endpoint.

Sample Size

We estimate that the primary outcome, verified smoking cessation rate at 6-month follow-up, will be 20% among the Standard Care group and 35% among the Extended Care group. With a sample size of 165 per group, the study will have 83% power to detect such a difference with a 0.05 two-sided significance level. The estimate of the Standard Care cessation rate was based on MGH TTS program outcome data. The effect size (35/20=1.75) was based on results of a recent meta-analysis, but increased to reflect project innovations.

Cost-effectiveness analyses

Cost-effectiveness analyses will be conducted with cost per quit as the main outcome to ensure maximum comparability with other published studies. Our principal cost-effectiveness outcome, marginal cost per quit, is estimated as follows: (Total costs of Extended Care - Total costs for Standard Care)/ (Total successful quits at 6 months for Extended Care -Total successful quits at 6 months for Standard Care). The major costs associated with the intervention are TTS time (based on hourly wage), the cost of the IVR service, the cost of providing a free 30-day supply (with 2 renewals) of pharmacotherapy to participants after discharge, and the cost of any additional counseling or pharmacotherapy used by participants. The major costs in the Standard Care arm that require tracking are the use of post-discharge counseling or pharmacotherapy. For both study arms we will track the portion of counseling and therapy costs (exclusive of the pharmacotherapy specific to the intervention) paid for by participants out of pocket versus by insurance. Prospective collection of cost information (for example TTS time) will maximize accuracy of our data. A secondary cost-effectiveness analysis will compute costs and quits under the intensive follow-up regimen whose effectiveness was documented in the Cochrane Review using published data and estimates of the human resources costs of intensive post-discharge follow-up. This will allow comparisons of the relative cost-effectiveness of the Extended Care intervention and the current standard of best practice.

RISKS AND DISCOMFORTS:

The potential risks to subjects are minor but include psychological distress of speaking with a counselor or answering the automated phone call’s questions about their smoking, and a loss of confidentiality of information regarding participant smoking status. In addition, those patients randomized to the “extended care” group that
distributes free pharmacotherapy may be subject to the risks of using NRT, bupropion, or varenicline.

**POTENTIAL BENEFITS:**

Participants in this study may benefit by being more efficiently connected to tobacco treatment resources, as well as acquiring pharmacotherapy more cost-effectively. As a result, they may be helped to quit smoking. Generally, there is nothing better for smokers’ health than stopping smoking. Potential knowledge to be gained from this work could help patients, doctors, and hospitals increase the number of tobacco users who receive treatment in the United States. Smoking remains the number one cause of preventable death in the United States.

**MONITORING AND QUALITY ASSURANCE:**

The principal investigator, Dr. Rigotti, will be responsible for monitoring the safety and effectiveness of this trial, executing the DSM plan, and complying with reporting requirements. Dr. Rigotti will supply a summary of the DSM report to the NIH on an annual basis as part of the progress report. This report will include descriptive reports of the participants’ sociodemographic characteristics, expected and actual recruitment rates, retention rates in each treatment condition, quality assurance and regulatory issues that arise since the last report, summary of AEs and SAEs, and any protocol changes. This report will also include the results of any effectiveness data analyses conducted.

**Data monitoring plan**

Participant data will be collected using paper and pencil records (participant questionnaires, progress notes from smoking cessation counselors) stored in a locked filing cabinet in a locked room, and electronic participant tracking spreadsheets stored on a secure server. Paper and pencil forms will be double entered into an electronic database and discrepancies will be resolved by the study coordinator. To prevent the loss of data, all electronic information is stored within the Partners Healthcare System, Inc. firewall, password protected, and anti-virus software enabled computer systems. Only study staff will have access to the study data on Shared File Areas. Participants will be identified on study forms and in the database by a participant number. Participant names and contact information will be stored in a separate file.

During the IVR intervention, we will provide TelAsk, the IVR vendor who will be conducting follow-up IVR calls, with patient names, phone numbers and date of discharge. Upon completion of the study, we will transmit the data back to our secure Partners shared drive. All patient data will be purged from TelAsk’s data files. Data will be transferred through a secure FTP (both to Telask and back to MGH). During the study, they will establish a secure website to view call results in real time, quit statuses and counseling requests.
Data quality (including visits completed during intervention window, data missingness, and recruitment rates) will be monitored monthly by the database manager, Dr. Susan Regan, and systemic data problems will be reported to the PI. Each smoking cessation counselor will audiotape 10% of their sessions to be reviewed by the project director, Dr. Sandra Japuntich, for adherence to the protocol. In addition, Dr. Japuntich will review 10% of the counseling progress notes for adherence to the protocol.

The primary outcome measure for this study will be 7-day point-prevalence abstinence at 6 months post-hospitalization verified by either saliva cotinine or a proxy corroboration of nonsmoking. We will also test for point-prevalence abstinence at 1 month post-hospitalization. In addition to smoking cessation, we are also interested in 2 intermediate outcomes: use of tobacco treatment during the 6 months post-hospitalization and the duration of tobacco abstinence post discharge from the hospital. Outcomes data will be analyzed by Dr. Yuchiao Chang, a biostatistician, using logistic regression and survival analysis. The alpha level will be set at 5%.

Interim data analysis will be conducted halfway through the trial and results will be reported in the annual NIH progress report.

**Safety monitoring plan**

The main risks to participation in the study include the potential for psychological discomfort during counseling sessions and previously documented side effects to the FDA-approved medications. We will protect against risks of psychological discomfort by using language that is meant to offer assistance and promote health, rather than demonstrate blame or guilt. In order to protect against risks associated with pharmacotherapy usage, the research assistant will contact the admitting physician to obtain approval and a formal medication order. In order to protect against risks associated with pharmacotherapy usage, all medications will have been prescribed by the patients’ attending physicians in the hospital. The 5 telephone calls after discharge will ask about medication side effects and offer patients the opportunity to be called by the smoking counselor to assess adverse events. In addition, written and verbal instructions will be provided to patients given medication to contact their primary physician and the research study staff in case of adverse effects of a medication. Patients' primary care physicians will be sent a short email or note to inform them of patients' study participation and medication choice. At the 1-month follow-up assessment call, the research assistant will screen for adverse events and inform the study coordinator, who is a nurse, of any concerns. Ultimately, the PI will review any serious adverse events and report them to the IRB and NIH.

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