Design Strategy for a Smoking Cessation Trial of Survival

Jonathan J. Shuster, Ph.D.

Abstract

Despite unequivocal evidence that smoking cessation is beneficial in terms of survival, there is at present no firm evidence that smoking cessation programs save lives. While they do increase quit rates, the collective evidence from randomized trials is inconclusive with respect to long-term survival. Withdrawal symptoms and the potential for harm when a subjects relapses after a prolonged period of cessation (e.g., 5+ years) might mitigate some or all of the benefits of the sustained quitters. This paper will review the key survival epidemiology and argue for a large randomized field trial of about 30,000 subjects, followed personally for 5 years and collectively for 15 years through the National Death Index. The intervention should be personalized, but reproducible through a treatment assignment algorithm. Personal coaching should be a major part of the intervention. Important short-term data on healthcare utilization should also be collected. Strong financial motivation for quitting (or prevention of smoking in the first place) is also presented. This paper is intended to motivate a large collective effort amongst the US Clinical and Translational Science Awardees to design the intervention and bring together the interested players to conduct the study. Clin Trans Sci 2015; Volume 8: 132–136

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Introduction

Arguably, one of the most important public health questions we have today is whether or not a well-crafted and reproducible smoking cessation program can save lives. This paper will lay out an argument for a very large field trial of this question, under a yet to be identified aggressive, personalized, but algorithmically based intervention plan, to define and evaluate a cessation program. Although smoking cessation unquestionably will increase one's life expectancy, the evidence from randomized trials that smoking cessation programs improve survival is weak at best. We shall argue in the next paragraph that at present no definitive answer to this question exists. While it is true that smoking cessation programs can lead to a higher long-term quit rate than no intervention, and those long-term quitters will unquestionably benefit, the majority of subjects will either continue to smoke or quit for a period of time before relapsing. Although we can find no firm evidence as to whether or not those relapsing after a prolonged period of cessation (e.g., 5+ years) are better or worse off than they would have been under continued smoking, it is certainly plausible that such subjects could be harmed. Not only have they suffered from withdrawal symptoms, but the extended gap from smoking might interfere with natural immunologic and physiologic defenses they have developed against the ill effects of smoking. They conceivably could be more vulnerable to the damaging impact of smoking than they would have been under continued smoking.

There have only been two large scale randomized trials of purely smoking cessation programs,^{1,2} where the participants have been followed sufficiently (e.g., 10+ years) to assess this question. The survival information is presented in *Table 1*. Neither training nor the nicotine patch had a statistically significant survival benefit over their respective controls. If one pools the experimental groups in the Lung Health Study,² the benefit does reach borderline statistical significance at $p = 0.036$. But this was a “second bite of the apple” as an earlier analysis of the Lung Health Study³ had no significant survival benefit for the intervention groups. The Lung Health Study is an extremely important trial, but it was not specifically designed to address survival as a major endpoint, and as such was not adequately powered to achieve a definitive result. We shall argue that their sample size for their

specific target population was off by a factor of at least 10 to properly address the long-term survival question.

In addition, a meta-analysis of multiple risk factor intervention studies by Ebrahim and Smith,⁴ where a smoking cessation program was part of the intervention, failed to find a significant advantage, despite other potentially beneficial additions to the intervention group. In fact, the authors concluded that not only was there no significant benefit, but the collection of studies was sufficient to reasonably rule out a relative benefit that exceeded 10%.

Based upon all of the available information, a reasoned position is that we should be in equipoise over the survival benefits of smoking cessation programs. This is not a contradiction of our belief in benefits of smoking cessation. The key question is “Are the benefits for the average individual in a smoking cessation program greater than the harms due to side effects of quit attempts or the drugs they use to help them quit?” Apart from the potential ill effects of late relapses, prior cessation research has been associated with relatively high failure rates and important adverse effects, whether the quit attempt is successful or not. Smoking cessation attempts have been associated with significant weight gain, even amongst those who relapse into resumption of smoking.⁵ In addition, a small study found a significant loss of sleep early in attempts to quit.⁶ A promising approach, varenicline (Chantix) was found to be associated with increased short-term cardiovascular risk.⁷ Due to the addictive nature of smoking, sustained quit rates are generally low. For example, in the Lung Health Study,² only 21.7% of the subjects randomized to a smoking cessation program were sustained quitters, while 5.4% of the controls were. Recently, West et al.⁸ found that Cytisine (golden rain acaeia) had a dramatic impact on 1-year continuous cessation rates (8.4% vs. 2.4% on placebo). While this is an exciting study, the quit rates are too low to consider Cytisine as a sufficient single intervention. It is therefore critically important to develop and test a new personalized intervention program for smoking cessation. This program should target entire families, their lifestyles, and deal with relapses and the side effects of cessation attempts.

A close analogy can be made with the challenge to cholesterol lowering drug research in 1992, when an editorial by Davey-Smith and Pekkanen,⁹ despite their belief that lower cholesterol is associated

Department of Health Outcomes and Policy, University of Florida, Gainesville, Florida, USA.

Correspondence: Jonathan J. Shuster (jshusterj@biostat.ufl.edu)

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Study	Usual care	Training	Training plus nicotine patch
British workers	130/731 (17.8%)	123/714 (17.2%)	–
US Lung Health	270/1964 (13.7%)	235/1962 (12.0%)	226/1961 (11.5%)

Successful quitter (continued smoker) 15-year survival: 0.846 (0.782).
 Entries are deaths/N (%).
 Odds ratio (95% CI) [*p* value] Training: Usual Care 0.89 (0.76–1.04) [0.13].
 Nicotine Patch: Placebo 0.96 (0.79–1.16) [0.66].
 Method: Mantel–Haenszel.

Table 1. Smoking cessation and mortality (14.5–20 years follow-up).

with better survival, suggested a moratorium on cholesterol lowering drug research be instituted. Fortunately, this did not happen, as a new approach using statins emerged shortly thereafter.

The motivation for another trial in this area is based on the following. (1) The past trials were, in retrospect, underpowered; (2) the past trials were not sufficiently tailored to the individual subjects; (3) new methodologies and ideas have emerged. In addition, the Lung Health Study targeted subjects with chronic obstructive pulmonary disease, whereas this trial would target the general population of 45–65-year olds, and thus will have more generalizable results. By collecting appropriate identifiers, it will be possible to complete the survival analysis with little added cost. The study would be active for 5–7 years and dormant until the survival analysis is completed at 15 years. While some may question the relevance of a survival analysis 15 years into the future, and that the methods may be obsolete by then, we counter this on three fronts. First, nearly 50 years after the Surgeon General's Report, we still have no definitive evidence that smoking cessation programs save lives. Second, the prevalence of smoking amongst adults is still about 20%, and has not declined substantially in the past 10 years. Finally, this study could have a unique economic component where in selected centers, we could assess the true medical costs versus savings associated with quit attempts within a randomized clinical trial.

Methods

Overall, we believe we should deal with this long-term smoking cessation trial as if it is being conducted to test a potentially curative cancer drug requiring US Food and Drug Association (FDA) approval. Such drugs require proof of a survivorship advantage. While the major statistical elements for the study design are contained in this section, to make this operational, one might begin by conducting a 1–2-year planning phase before the trial is initiated. This planning phase would develop a consensus intervention strategy, based on the top cessation and addiction experts, and conduct a pilot study at the potential sites to establish feasibility. The planning phase would also determine a central operations center, statistical center, data management center, and survey center. Strategies for training personal coaches would also be developed. The outcome of this planning phase would be a clinical trial that would be ready to be conducted.

The study would be operationalized as follows. Subjects who meet the eligibility conditions, which include an expressed desire to quit, would be randomized (and as couples, where both spouses qualify). Controls should receive written material on cessation.

Possible platform for research

The Clinical and Translational Science Consortium (CTSC) is an excellent platform for this research. The University of Minnesota,

a consortium member, serves as the Data Coordinating Center for the Lung Health Studies. The consortium members also have exceptional outreach programs that can readily secure all of the needed expertise in addiction, quality follow-up, and recruitment of personal trainers. Investigator meetings could be economically conducted when tied to national CTSC meetings.

Planning parameters for 15-year survival

To obtain truly representative planning parameters for a control group and a treatment group, we need to make several assumptions. First, we need to assess the survival probability for the eligible subjects in the study under continued smoking and successful cessation. Second, we need to make realistic assumptions about the quit rates for both intent-to-treat randomized groups. Finally, we need to consider the fraction of subjects we shall assign to each treatment group. The study needs to be planned so that if significant, the evidence is convincing. Therefore, we chose a low type I error rate of $\alpha = 0.01$ (two-sided) and high power $\pi = 0.90$.

For eligibility, we believe the age window of 45–65 is ideal. Since power is driven by events (deaths), and since we wish to have a large impact upon survival if the intervention is successful, we feel this is close to optimal. Younger subjects have much lower risk, and older subjects will have substantial competing risks. There are two sources we shall tap to make our estimates of survivorship. The Nurses Study¹⁰ provides relative risk information, smoking rates, prevalence rates for never smoked, former smoker, and current smoker, and the time it takes for quitters to equalize their survival risk to never smokers. US Mortality tables (See Table GMWK23R_2007 at the National Vital Statistics System website¹¹ for details) provide annual death rates in 10-year age windows. While it may be argued that the Nurses Study targets females, there is no comparable cohort that provides better information, and we expect differences with the general population on the issues contributing to the power analysis to be relatively unimportant.

1. Relative risk for mortality: current smokers to the general population. According to the Nurses Study,¹⁰ the estimated relative risks for current smokers (former smokers) to never smokers are 1.87 (1.29), respectively. The estimated baseline prevalence rates for current smokers (former smokers)[never smokers] are 30.1%(26.3%)[43.1%], respectively. Therefore, the relative risk for current smokers to the general population is estimated at $1.87 / \{1.87 \times 0.301 + 1.29 \times 0.263 + 1.00 \times 0.431\} = 1.405$.
2. Death rates for smokers: the annual mortality rates per 100,000 in the general US population in 2007 were 420.9 (877.7)[2011.3] for ages 45–55(55–65)[65–75], respectively. For simplicity, we assume we will accrue equal size cohorts of 45–55 and 55–65, followed for 15 years. A conservative but simplifying assumption, due to increasing hazards over

Control contamination	Experimental contamination	Control survival	Experimental survival	N 1C:1E	N:1C:2E	N:2C:1E
5%	75%	0.785	0.798	59,600	67,500	66,600
5%	67%	0.785	0.803	29,400	33,500	32,700
5%	60%	0.785	0.807	19,100	21,800	21,600

Successful quitter (continued smoker) 15-year survival: 0.846 (0.782).
N XC:YE is allocation of X controls per Y experimental.

Table 2. Total sample size requirements for various scenarios ($\alpha = 0.01$ two-sided, 90% power).

time, is to do the calculations as if all of the 45–55-year olds (all 55–65-year olds) are 50 (60) years of age when accrued. This avoids imputations for individual years. For smokers, these annual rates will be multiplied by 1.405, the estimated relative risk for smokers to the general population, to estimate the annual and total death rates for the smokers.

- Death rates for successful quitters: an important piece of information from the Nurses Study¹⁰ is that the authors estimate that it takes 12–14 years for the death hazard to revert to that of a nonsmoker. To be conservative, we shall use 14 years as the risk match time. If the relative risk for quitting smokers to never smokers declines at a rate of 4.37% per year, then after 14 years, these subjects will have a relative risk declining from 1.89 (See A above) to 1.00 in year 14. We will assume no further decline in year 15.
- Fifteen-year survival rates calculated from the above assumptions: continued smokers (78.2%), successful quitters (84.6%). Table 2 provides some information on the necessary sample sizes under various scenarios for “contamination rates,” where subjects assigned to quit relapse and where control subjects actually manage to quit. We used 5% as the contamination rate for controls, as was observed in the Lung Health Study. We also look at allocation rates to the two groups (1–1, 2–1, and 1–2).

Final sample size projection (about 30,000 total)

Since the Lung Health Study had contamination rates of 5% (controls who quit) and 78% (intervention subjects who relapsed), and since our projected intervention will be much more intensive, we felt it reasonable to use contamination rates of 5% and 67% (one third randomized to the cessation program will be sustained quitters) for this study, leading to a sample size of about 30,000, depending somewhat upon a yet to be made decision on allocation. See Table 2 for details.

Logistics for the randomized trial

If we presume that 30 of the 61 CTSC members take part, the accrual requirement would be about 1,000 per member. Further, if we assign 50 subjects per personal trainer, we would require about 7–13 trainers per CTSC member, depending upon the allocation ratio to controls. According to the CDC,¹² 68.8% (52.4%) of current adult smokers express a desire to quit (tried to quit in the past year). The final analysis would need to account for a minor amount of clustering for multiple smoking couples and for personal coaches.

There are two logistical questions that need to be addressed before the study is launched:

Q1: Do the controls need to know they are on a randomized study? If the baseline survey is done as a separate study,

where the subject is asked for death identification information, whether or not they wish to have a personal trainer help them quit, if selected via a lottery, and for release of economic healthcare utilization data for statistical purposes, we believe that the answer to this question is no, with the return of the completed surveys as adequate consent. A second study would create a lottery for those indicating they wish to quit with the help of a personal trainer. This will help the investigators to conduct a truly intent-to-treat analysis amongst those surveyed, who indicate a willingness to use a personal trainer.

Q2: What allocation of subjects, intervention to control, is ideal? As seen in Table 2, allocations of 2:1 in either direction increase the sample size requirements by only about 10%. More disparate allocations lead to major increases in sample size requirements. Since controls can be obtained at a much lower cost than intervention subjects, a study of two controls per intervention subject would lower the costs of the study by a substantial margin. However, an allocation of two intervention subjects per control has the potential to save more lives if the intervention proves to be effective. It is unclear at this time how this trade-off might be resolved by the potential stakeholders.

Accommodation for highly resistant smokers

If this study is launched, we shall find a significant fraction of subjects will relapse multiple times into smoking. For this study, it is recommended that those in the intervention group that relapse twice be offered an intensive secondary randomized trial of reducing consumption with personal coaches. Apart from contributing to the main study, a more limited goal would be measuring tobacco consumption and comorbidities of the competing strategies

Discussion

Our proposal is to complement, not supplant short-term studies on new ways to increase short-term quit rates among smokers. That is a very important line of research in of itself, but these studies ask completely different research questions from what we propose. However, those short-term studies should collect death identifiers so that random effects meta-analysis of long-term survival outcomes can be accomplished in the future.

If we had tried to replicate the Lung Health Study, focusing on healthy subjects with baseline ages 35–60 (rather than 45–65), assuming a 67% contamination rate for those assigned to the experimental arm and the same operating characteristics, a 1–1 allocation study would require 66,000 subjects (33,000 per group). Using the same methods as our own calculation, we would project the 15-year death rate for smokers at 13.7%, virtually identical to the

death rate in the Lung Health usual care group (See Table 1). This requirement is more than 10 times that of the actual lung Health Study and about double the requirement for our proposed study.

The limitation of our approach is that if a difference is found, it will not be possible to infer which of the many interventions is effective. There is considerable precedent for aggressive multiple risk factor interventions, including the component studies in Ebrahim and Smith,⁴ where a smoking cessation program was just one part of the intervention. A breakthrough study of the Pediatric Oncology Group¹³ pitted surgery plus a large battery of chemotherapeutic agents against surgery alone to ask the question as to whether chemotherapy has any efficacy. They learned that it did, but the study could not tease out which agents were effective. Factorial studies cannot resolve this without a major increase in sample size, as single interventions will not be expected to produce major differences. In the smoking cessation design, a factorial study would have an added complication, in that eligibility for each intervention would be targeted to a well-defined subset, losing the rectangular nature needed in a true factorial design.

Motivation for participation

A major obstacle to success might be low participation rates by the subjects. A major tool to encourage subjects to take part is financial. Let us assume the following: current price per pack of cigarettes is C , average annual inflation price of cigarettes is R (decimal fraction), number of packs consumed per day is P , and the number of life years remaining for the subject is Y . Then the lifetime savings associated with quitting is given by

$$S = CP\{(1 + R)^Y - 1\}/R. \quad (1)$$

At $C = \$7$ per pack of cigarettes, assuming a conservative annual inflation of $R = 0.04$, a one-pack-a-day smoker ($P = 1$) would save \$76,000 over a $Y = 20$ -year remaining lifespan or \$143,000 over a remaining $Y = 30$ -year lifespan. This is even more impressive to prevent initiation of smoking in a teenager. Over a $Y = 50$ -year lifespan, the savings would be \$390,000. Each of these subjects could win a lottery with no luck involved, if they quit or never smoke in the first place.

While this research strategy is expensive and would take years to accomplish, this long-term investment would have enormous potential to save lives. The study will also provide opportunities to ask well powered secondary questions on (a) relative health care utilization and (b) prognostic factors as to what subsets benefit most versus least from the program. One example, motivated by the association between quit attempts and weight gain,⁵ would be to study the relative risk of the intervention as a function of baseline body mass index. Specifically, do obese subjects benefit less than nonobese subjects from the intervention?

The National Institute of Health has precedents for investing appropriately in very large trials of public health priority. Two examples are the Women's Health Initiative,¹⁴ where 64,500 women were to be randomized to hormone replacement strategies, and the National Lung Screening Trial,¹⁵ where over 53,000 subjects were randomized to competing screening strategies. The bottom line is that if we do not do a definitive study of this nature, will we be able to say definitively in 2030 that a life-saving smoking cessation program exists and if so, what it is?

It is of interest to note that Alpert et al.¹⁶ have provided an interesting analysis leading to a conclusion that population-based intervention studies might not be an effective way to

attack smoking cessation. Ironically, their negative assessment is actually totally in line with our own approach. We quite agree that a simple intervention, such as nicotine replacement therapy, would not be adequate in of itself. We agree with these authors that a highly personalized approach is what it will take to be successful. While our approach is highly personal, it also needs to be algorithmically based, so that it is reproducible. In other words, the characteristics of the subject and family would determine what the initial intervention would be.

This study could form a precedent for the CTSC to get involved in large clinical trials on a national scale. Interventions that do not involve product development would be especially welcome in this arena. Needless to say, these efforts would require separate grant funding.

One final note is that long-term survival studies, such as this one, should not presume proportional hazards, if a reasonable model can be postulated under the alternative hypothesis as to how the trends in hazard ratios change over time. For example, in hypertension trials, the relative instantaneous benefit of a drug treatment over a placebo under the alternative hypothesis will likely decrease over time, making sample size needs greater than the sample size that one might calculate under proportional hazards. Although the methods in this paper are specific to smoking cessation, they can be adapted to other trial scenarios such as this.

Conclusion

The Clinical and Translational Science Consortium is well-placed to develop and test an aggressive algorithmically based but personal smoking cessation program with the major objective of improving long-term survival rates for current smokers.

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