Author's response to reviews

Title: Improving adherence to web-based cessation programs: a randomized controlled trial study protocol

Authors:

Amanda L Graham (agraham@legacyforhealth.org)
Sarah Cha (scha@legacyforhealth.org)
Nathan K Cobb (ncobb@legacyforhealth.org)
George D Papandonatos (gdp@stat.brown.edu)
Ye Fang (yfang@legacyforhealth.org)
Raymond S Niaura (rniaura@legacyforhealth.org)
David B Abrams (dabrams@legacyforhealth.org)

Version: 2 Date: 16 January 2013

Author's response to reviews: see over
January 16, 2013

Doug Altman, Curt Furberg, Jeremy Grimshaw and Peter Rothwell
Editors-in-Chief
Trials

Dear Editors:

We appreciate the very thoughtful and detailed review of our manuscript titled Improving adherence to web-based cessation programs: a randomized controlled trial study protocol. We have modified the manuscript in several places to address the questions and comments noted by the reviewer, and provide our response to each item below.

Thank you for your consideration.

Regards,

Amanda L. Graham, PhD
Director, Research Development
Schroeder Institute for Tobacco Research & Policy Studies
American Legacy Foundation

Associate Professor (Adjunct)
Department of Oncology, Georgetown University Medical Center
Division of Cancer Prevention and Control, Lombardi Comprehensive Cancer Center
1. The authors describe this as a 2 (NRT, no NRT) * 2 (SN, no SN) factorial design, but this doesn’t seem to reflect the way they are setting up the hypotheses and powering the study – it seems instead it is a straight forward 4-group trial of WEB[1], WEB+NRT[2], WEB+SN[3], and WEB+NRT+SN[4], with the 5 comparisons of interest as 2, 3, or 4 vs 1, and then 2, 3 vs 4. For a standard 2*2 factorial, the main comparisons would be for the main effect of NRT [2+4 vs 1+3] and the main effect of SN [3+4 vs. 1+2], and the study would implicitly assume no interaction in the power calculation. Here the authors actually are explicitly including a small interactive effect (since 8% + 6.5% for the individual effects is less than the 16% assumed for the combination), and they have powered the study at a 1% level of significance to adjust for the 5 stated primary comparisons. So I think it will needlessly confuse readers introducing the terminology ‘2*2 factorial’?

**RESPONSE:** Although our study design is 2x2 factorial in nature, the proposed analytic plan is indeed non-standard for such a design. The reason is that we are primarily interested in whether the combination of both strategies exerts a more powerful effect on adherence than either strategy alone, rather than testing the presence or absence of a SNxNRT interaction whose interpretation depends on the scale of measurement. For example, our preliminary/pilot data suggested that we should expect quit rates of WEB=10%, WEB+SN=16.5%, WEB+NRT=18% and WEB+SN+NRT=26% at 9 months post-randomization. Such quit rates suggest a small synergistic interaction in the probability scale (since 6.5%+8.0% for the individual SN and NRT treatment effects is less than the 16% assumed for the SN+NRT combination therapy), which actually becomes a weakly antagonistic interaction in the odds scale typically used for modeling the data (the SN vs. no SN OR is given by 1.60 when WEB+NRT is the reference group vs. 1.78 when WEB alone is the reference group, leading to an SNxNRT interaction OR=0.90). Although statistical interpretation of the interaction depends on the scale of measurement, interpretation of the pilot estimates from a clinical perspective is unambiguous: the combined treatment has the most powerful effects on adherence. This is the appropriate inferential target and is addressed by our choice of contrasts. Testing for interaction is of interest from a statistical perspective, but is of less interest from a clinical perspective. However, the clinical question does require the use of a 2x2 factorial design, even if it is not based around testing of the interaction effects, as it is the only design that allows us to estimate a combined treatment effect.

We had previously alluded to our interest in estimating an SNxNRT interaction in our Aims section by describing SN and NRT treatments as “two separate, but potentially interactive, strategies to improve adherence to the evidence-based elements of cessation treatment.” We have now deleted references to estimating interaction effects, as they do not present a valid inferential target.

2. The description of the ‘social network integrators’ isn’t that clear. How many of these integrators are intended to be recruited? There is a target of 2,000 participants going to be randomised to the two social network arms – how many can an integrator deal with? The description on page 21 talks of the ‘use of dedicated staff’ and ‘full time professionals’ – what is the time commitment expected from these integrators?

**RESPONSE:** In the description of the WEB+SN intervention on Page 12, we indicated that two Integrators have been recruited for the study (“Two former smokers who are well-known, longstanding, active members of the community serve in this role”). We have reiterated that the study involves 2 integrators in the last paragraph on Page 12 where we describe the selection process of Integrators. We have also added text on Page 10 at the end of the Recruitment section that states “Recruitment volume is capped at a maximum of 10 new enrollees per day to ensure a manageable workload for intervention and research staff throughout the study period.”
clarify the time commitment of Integrators in the study, we have added text on Page 12 that states “Each Integrator spends approximately 1–2 hours per day in this role.” While many online communities do hire dedicated full time professionals and paraprofessionals to serve as Integrators or peer moderators – managing communities of hundreds and even thousands of members – funding constraints only permit us to engage two individuals in this role.

3. Also, how long does someone who has successfully quit smoking stay involved in an on-line community devoted to helping people quit smoking? Does there come a point where they consider themselves to be an established non-smoker and of little or no further interest in smoking and its culture and issues?

**RESPONSE:** Unfortunately there are no published reports on the average duration of engagement in an online cessation community, although the distribution of most systems of this nature tends to follow a log-log distribution with rapid loss of participants up front [1]. As is seen in most support groups, behavior after cessation appears to be heterogeneous, with some participants continuing to participate to avoid relapse, others continuing to participate to provide support, and many others moving on. Based on prior work by our group on a similar system (QuitNet.com), we know that individuals who have been abstinent for years – much like our Integrators – remain actively involved in an online smoking cessation community. While these individuals may be uncommon, they provide structural “glue” within the network [2]. One reason behind this continued engagement is the notion of “paying it forward” by providing assistance and support to other smokers struggling to quit or maintain abstinence. There is also a strong culture that emerges in online social networks where some former smokers who play an active role in the community are given “elder” status and looked to as “experts.” This form of social status can be a powerful motivator to remain engaged in an online community long after someone has quit smoking. We note that long term participation in online communities associated with social status is commonly observed across other communities – for example, software product support communities and video game communities.

4. The authors discuss ‘contamination’ (page 21) and sensibly see that the uptake of either NRT in groups not randomised to free NRT for the initial 4 weeks, or the participation in a social network online for those likewise not randomised to this intervention as ‘unavoidable and part of the nature of conducting dissemination work’. However, the authors go on to point out that a very small percentage of participants engage in the community and use pharmacotherapy as directed – so doesn’t this make the influence of any contamination proportionally more rather than less of a worry? That is, if uptake was universal a small amount of contamination wouldn’t matter that much, overall?

**RESPONSE:** We regret that our wording was unclear and have modified text in the first paragraph of the Limitations section (Page 24) as follows: “In an explanatory randomized trial [104] use of unassigned treatments may be considered “contamination”. However, in the context of a web-based pragmatic randomized trial such as this, the use of unassigned treatments is unavoidable but is expected to be minimal. That is, we anticipate that a small proportion of WEB or WEB+SN will use NRT on their own without any prompting or intervention, and a small proportion of WEB or WEB+NRT will engage in the community without any prompting or intervention. The aim of our research is to test the effectiveness of two strategies to increase the proportion of participants who adhere to all components of cessation treatment over and above the “usual care” rates of use. Our power analysis, measurement instruments, and assessment protocols are designed to account for the ways in which individuals use these resources in the real-world.”
5. Also, isn’t there potentially a major issue in that 4 weeks of NRT isn’t perhaps long enough? What was the 4 weeks based on? Cost, or evidence of effectiveness?

RESPONSE: As the reviewer implies, nicotine replacement therapy typically lasts 8-12 weeks depending on the product type. Our decision to offer a 4-week starter kit rather than a full 8-12 week supply of product was informed by several studies that have demonstrated that (1) adherence to NRT remains an issue even when participants are provided a full course of therapy [3] (i.e., in the absence of directed efforts to improve adherence) and that (2) sending more free NRT to smokers does not necessarily translate into enhanced duration of use [4] or chances of quitting and remaining smokefree [5]. We are interested in examining whether providing free NRT increases initial uptake (i.e., any use), and whether the web-based information and resources (WEB) and/or proactive outreach from the social network (SN) increase overall adherence, including purchase of additional product beyond the free supply. We have added text to the Group 3 (WEB+NRT) intervention section (Pages 13) to clarify our rationale for providing 4 weeks of NRT.

6. It would be useful to understand better the ‘website utilisation’ metrics – they seem naively to be based purely on time-based ‘exposure’ measures – not on whether the important content has been received, understood and acted upon. For example, if someone is highly motivated and finds the right information quickly or establishes an important social network quickly, there ‘website utilisation’ might seem very modest (albeit ultra effective) – whereas someone online for a long time might just be reflecting an unsuccessful period of usage? That is, these metrics may be non-linear in their relationship with outcome?

RESPONSE: The general website utilization metrics referenced in this comment are indeed primarily exposure based metrics. While limited, they are the standard metrics of engagement that are used to determine the “dose” of intervention received [6]. We have made minor edits to the descriptions of the various utilization metrics described in the Treatment Adherence section on Pages 18 and 19 to make explicit to the reader that we track and analyze a broad range of utilization metrics, ranging from the recording of all content viewed to time-stamped recordings of the creation and dissolution of friend ties. We also point to the reviewer to the Intervention Satisfaction and Quit Methods/Pharmacotherapy Use which describe additional assessments of treatment “exposure.”

7. The authors clearly indicate that biochemical verification of smoking status isn’t feasible on a national sample enrolled through the internet – that is understood – but the proposed random sample of 10% of self-reported quitters with an established protocol for verification by a significant other still presumably relies on self-report? Was there no possibility of conducting a separate substudy on e.g. 5% using biochemical verification?

RESPONSE: For large, population-based trials with low demand characteristics, self-reported smoking status is a commonly accepted outcome measure. Also, verification of abstinence by a significant other is well-established and accepted within addictions research when biochemical verification is not feasible and/or unnecessary. We have added the following text to Page 9 in the Study Design section to clarify why biochemical verification is unnecessary in this type of trial. “Biochemical verification of abstinence is not feasible on a national sample enrolled through the Internet. Furthermore, misreporting of abstinence is expected to be low for several reasons: low demand characteristics of the interventions, the use of a proactive recruitment strategy to recruit a representative sample of smokers that do not have special consideration that might elicit misreporting, the fact that participation is completely under the control of the participants, and the use of an extended, 6-month post-treatment follow-up period [7-10].” We have attempted to synthesize an extensive discussion in the paper.
by the SRNT Subcommittee on Biochemical Verification in this revision, and hope our modifications provide clarity to the reader.

8. In terms of the exclusion criteria, are these all solely based on self-report too? Would all potential participants reliably know and report any of these contraindications to NRT?

**RESPONSE:** Eligibility screening is based on self-report, modeled on the over-the-counter sale of these products. We have modified text in the Recruitment section on Page 10 to list the specific items that are administered during online eligibility screening. Screening questions specific to the three contraindications for nicotine replacement therapy (pregnant or breastfeeding, recent cardiac problems, current nicotine replacement therapy use) are based on NRT product information sheets included in the nicotine patch, gum, and lozenge packages that users are instructed to read to determine if it is appropriate for them to use these over-the-counter products. We believe that our screening is likely more stringent than the self-screening that is performed when these products are purchased under FDA regulation at a local pharmacy, and is consistent with best practices in clinical settings such as telephone quitlines.

9. The authors should clarify the nature and rapidity of the feedback and professional guidance that is going to be available – they say the website is open 24/7, but later say ‘Administrative support is available and all questions are addressed within 2 business days’ – so is this just about technical internet issues, not about quit questions etc?

**RESPONSE:** We have modified the description of the Social Support components of the WEB program on Pages 11 to address this concern (last sentence) and to improve the readability of this section. Text reads as follows: “The Re-Learn Support section emphasizes the importance of social support in the cessation process and provides guidance on how to solicit helpful support from family and friends. Members can also participate in the BecomeAnEX community. Online communications can take the form of a personal message sent directly between members, a public post on another member’s profile page (“wall”), a discussion forum post, a forum reply to a previously posted message, or comments on a blog post. The site has over 2,000 user-initiated discussion forums and hundreds of messages are posted in the community each day. Other social support elements in the site include the ability to invite contacts from a personal email list to join the site, to search by member name within the site, and to search for and read user blogs. Weekly clinical support blogs are posted by a tobacco treatment expert from the Mayo Clinic. Clear guidelines about appropriate community participation are provided. Administrative support for technical issues is available from the BecomeAnEX community manager and all questions are addressed within 2 business days.”

10. Page 19 – the authors seem to be committing to formal statistical tests of baseline imbalance between the randomised groups. This is considered poor statistical practice – imbalances are to be expected and by definition of randomisation are chance events. It is more appropriate to identify a priori what covariates are known or likely to be strongly associated with the outcomes, and then adjust for them regardless of their distribution in the experiment at hand.

**RESPONSE:** We agree that our study’s large sample size (N=4,000) makes it unlikely that finite sample randomization imbalances will be much of an issue and that formal statistical testing for such imbalances may lead to too many between-group differences being declared significant due to too much power for the omnibus Chi-square or F test. At the same time, we are field testing new psychometric scales whose distributional
properties and relationships to smoking outcome are not known a priori. Based on this suggestion, we will base our evaluation of the success of the randomization plan in achieving covariate balance across arms not on significance levels per se, but on effect sizes estimates (i.e., standardized differences between group means).