Author's response to reviews

Title: Nicotine patches and quitline counseling to help hospitalized smokers stay quit: A factorial design

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Author's response to reviews: see over
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Editor, Trials

Dear Editor,

Enclosed please find the revised version of MS: 1458052083619038, “Nicotine patches and quitline counseling to help hospitalized smokers stay quit: A factorial design.” We want to thank the reviewer for a careful reading of the paper and the helpful comments. We have modified the paper in response to the comments. Here we summarize our response.

1. P (age) 3, p (aragraph) 1, l (ine) 6. Since [or] logically includes [and], suggest dropping [and/]. Also P 17, p 2, l 10. Also P 22, p 5, l 17. Done

2. P 3, p 2, l 1. Replace [N] by [n] and insert a space on either side of the [=] sign to read [n = 1640]. Done

3. P 4, p 3, l 1. Include the date of registration and the date the first patient was randomized if that has happened. Done

4. P 5, p 2, l 2. Replace [recent] by [2007]. The word becomes less relevant with time while the date does not. Done

5. P 5, p 3, l 1. Delete [in order] in front of [to] as the words are redundant in English. Done


7. P 6, p 1, l 1. Delete [only] as it implies an unstated expectation. P 21, p 2, l 8. We removed “only” and changed the wording.

8. P 6, p 3, l 5. Rewrite as [p < 0.01]. Done

9. P 6, p 3, l 5 to 7. Can this be referenced? We included the reference Brandstein et al. 2010 SRNT presentation.

10. P 6, p 4, l 1. Replace [significant] by [important]. Reserve significant for a statistical context. Done

11. P 8, p 1, l 5. Suggest that the block size NOT be listed as this provides those who make decisions about eligibility of patients with information to anticipate the next allocation. This has been shown to create bias. The block size does not need to be published until the study is being written for final publication. The fact of blocking is desirable. Done

12. P 9, p 4. This sample size assumes an additive model. If there is any interaction it likely will not be detectable unless it is much larger that the main effects. This feature should be mentioned. Are the 7% effects actually clear as what can be seen in the literature? It would be good to R them. The sample size does assume an additive model since we have no basis on which to predict an interaction. The estimated effect size was determined from the pilot work that was conducted as part of Dr. Brandstein's dissertation. This has been clarified in the text.

13. P 10, p 1, l 1. Is there evidence that the variance inflation for clustering is around 10% for these two factors? Provide a R if you can. What software was used to calculate the sample sizes? There have been no studies that specifically measure the clustering effect in these kinds of studies. Hence, our estimate of the likely variance inflation is a best guess, although it is an informed guess. It seems likely that subjects at a hospital will tend to vary from those at another in unforeseen ways. However, it is important to remember that the study design calls for randomization by individual and the sample size is 1,640, far larger than other studies that have found an effect with hospitalized smokers. We have included a
statement that we used the software R to calculate the sample sizes.

14. P 10, p 1, l 3. Suggest including how big the effects need to be in this subgroup to show they will be clinically important as well as statistically significant. **The subgroup of subjects who are admitted due to cardiovascular or pulmonary disease is likely to be the largest single subgroup. However, our design is not set up to detect differences in effect size within this subgroup. The examination of the moderating effect of diagnosis on intervention will rely on the pooled data from the projects in this U01 (i.e., CHART). Our sample size overall is based on an estimated 40% increase in quitting success for each single intervention (counseling or nicotine patches) and a 60% increase for the combination intervention (counseling plus nicotine patches). These differences would be both clinically meaningful and statistically significant.**


17. P 12, p 2. Provide a R for the system used. **This system was developed in house, so there is no reference for it. We have clarified this in the text.**

18. P 13, p 2, l 3. Are the number of calls recorded and will they be used for exploratory analyses? **All calls are recorded and could be used for exploratory analysis.**

19. P 13, p 3, l 4. Try to make your language gender neutral by replacing [his/her] by [their] or some other neutral phrase. **Done**

20. P 14, p 4, l 2. Rewrite as < 10. **Done**

21. P 15, p 2, l 6. Provide a R to CHART measures. This R could also be used on P 16, p 1, l 1 and p 3, l 1. **Done, we have referenced Riley et al. in the same issue.**

22. P 15, p 2, l 7. Replace [is] by [are] since data is a plural word and it is used correctly on the same P. **Done**

23. P 17, p 3, l 1 and 2. Delete [(this issue)]. **Done**

24. P 17, p 3, l 3. Include the name of the company and its location in PA. What is known about the reliability of the cotinine analyses for this company? **We included the location of Salimetrics and a reference to their description of the high sensitivity salivary cotinine quantitative enzyme immunoassay. The article by Riley, et al. addresses the issue of the reliability of the company, since most of the CHART sites will use this lab.**

25. P 19, p 1 and 2. Provide the software that you plan to use for the overall analysis and the handling of missing data. **We’ve added a statement about using SAS 9.2 for analysis and we’ve included references for the theoretical handling of missing data.**

26. P 19, p 1, l 4 and 5. Since your study is not powered to detect an interaction, this should be mentioned here as well in the discussion. **We did clarify that the study was not powered to detect an interaction. However, since we were not hypothesizing an interaction, it seemed unnecessary to repeat this in the discussion.**

27. P 19, p 2, l 6. Provide a R for the sensitivity analyses being proposed. **Done**

28. P 20, p 1, l 2 and 3. Since this subgroup is smaller than the sample size for the entire trial, this effect will not likely be detectable statistically unless it is synergistic and much larger rather than moderating. **The subgroup is indeed smaller and the study is not powered to find differences within this group for this project. As mentioned above, the examination of the**
moderating effect of diagnosis on intervention will rely on the pooled data from the projects in this U01 (i.e., CHART).

29. P 20, p 2, l 8. No measure of utility has been proposed so far in the paper, so how will you compute the utilities to get the QALYs? Provide a R for this. Also the comparison of each active group vs control does not take advantage of the hidden replication in the design and they are correlated so should use some variant of Dunnett’s test in their analysis. Alternatively the 3 estimable contrasts could be used in the economic analysis, although the effect of the interaction is likely not going to be detectable statistically. It is true that we did not propose to measure the QALY for the individual by using measures of utility such as reported well-being. We intended to evaluate the outcome from the patient perspective using quality of life weights based on the literature such as the model proposed in Russell et al. 2001. We have clarified this in the text and added the reference. We will control for family wise error by using Hochberg’s step-up procedure to ensure a family-wise error rate/composite type 1 error rate of < 0.05. We have clarified this in the text and added the reference.


31. P 21, p 3, l 3. Delete [significantly]. Significance is a statement about a question, not part of it. Also P 22, p 1, l 3 and p 2, l 2 and p 3, l 1. Done

32. P 21, p 3, l 2 to 4. The viewpoint of the economic assessment has not been mentioned and should be. The paragraph referred to was about what made this study innovative, which is the factorial design. Since the economic assessment is not the innovation, we did not change the paragraph. However, we do mention the economic analytic perspective on the previous page under secondary aims.

33. P 23, p 1, l 2. Replace [efficient] by [effective]. No methods are provided to measure efficiency. Done

34. P 23, p 2, l 4. No mention has been made about the DSMB structure, membership, data access and reporting and should be. This information will be included in the Riley et al., since the same DSMB is applicable to all the CHART projects.

35. P 25, R 2, l 3. Insert [(5)] after [25]. Done

36. P 25, R 3, l 2. Insert [(5)] after [10]. Done


38. P 25, R 5, l 3. Insert [(1)] after [93]. Done

39. P 26, R 13 appears to be correct. OK

40. P 26, R 14. Insert the date of last access for online documents as they can change. Done

41. P 26, R 19 appears to be correct. OK

42. P 27, R 24, l 3. Insert [(5)] after [36]. Done

43. P 27, R 26. My copy is NOT published by Wiley. I have [Arnold, Holder Headline Group, London England and co published by Oxford University Press Inc, New York NY.]. We checked our copy and it is published by Wiley, so we did not change the reference.

44. P 27, R 27, l 3. Insert [(1)] after [11]. Done

45. P 27, R 28, l 1. This is the second edition and replace [Jersey] by [York]. We checked our copy and it was published in Hoboken, New Jersey so we changed the reference to reflect that.

46. P 27, R 29, l 2. Insert [(421)] after [88]. Done
47. P 28, R 30 appears to be correct. OK

48. P 28. Somewhere the paper should note that the reporting of the trial should follow the CONSORT guidelines and reference them. Done—on P16 we included the reference Schulz et al. 2010 article in Trials on the CONSORT 2010 Statement.