Author's response to reviews

Title: A Polypill for primary prevention of cardiovascular disease: A feasibility study of the World Health Organization

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Author's response to reviews: see over
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A Polypill for primary prevention of cardiovascular disease: A feasibility study of the World Health Organization

Dear Editor-In-Chief, the Trials journal

We thank you and the reviewers for the constructive comments and the opportunity to improve and resubmit our manuscript. Please find below, a point-by-point response to the reviewers' comments. We hope this revision meets your acceptance.

Sincerely,
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Reviewer: Matthew G Law
Reviewer's report:
Major Compulsory Revisions
1. I don't understand why changes in variables from baseline aren't analysed (Table 3). This would be a more powerful endpoint. The statistical methods does say that changes in variables were compared, but this doesn't look the case in Table 3.

Response: The changes from baseline were indeed analyzed (See Table 3, currently Table 4), as stated in the Methods. The p-values represent the significance of the differences in risk factors change between the study arms. To make this clear, we revised Table 3 (Currently Table 4) to include the baseline and exit values of the CVD risk factors as well as the change from baseline.

2. The lack of confidence intervals is a major omission

Response: We have added 95% confidence intervals

3. I think this trial does raise some very interesting questions about how you would design a large polypill trial in developing countries. If you recruit a high risk population, as in this study, there is clearly a risk that by having the control arm patients in regular follow-up that they will get given what are known effective interventions (as in this pilot). Even in you placebo control, regular monitoring of blood pressure and lipids would result in the same treatment interventions. So it seems to me that the options are either not to monitor (as suggested by Wald
Law), or to recruit a low risk population (in which treatment on risk factors would be much less prevalent). This really isn't discussed at all, which is a pity.

**Response:** A new paragraph discussing these options has been added to the Lessons Learned section (Page 11).

4. The authors conclusion - "we did not detect the anticipated CVD risk factor improvements..." - seems a bit harsh to me. You did see major improvements in BP, TC and 10-year CVD risk - the problem is you treated the controls as well and got similar improvements in those patients!

**Response:** We agree with the reviewer. We have reworded the abstract, especially the conclusion which now reads "Marked risk factor reductions were observed in the Polypill group. However, similar reductions were seen in the Standard Practice group. The benefit of the Polypill in our trial did not exceed that of Standard Practice."

5. I don't like the p-values in Table 1. I thought the consensus these days was that these are uninterpretable, and shouldn't appear?

**Response:** We deleted the p-values from Table 1

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Reviewer: David Wald

**Major Compulsory Revisions**

1. The trial is uninformative on risk factor reduction because the comparison group (standard treatment) also received unspecified cholesterol and blood pressure lowering treatment. The individual treatments and doses used in the standard care arm are not reported and without this there is no basis on which the reader can see what the expected difference in cholesterol and blood pressure would be. The information in Table 2 (giving the proportion of patients in each arm receiving statins or antihypertensive treatment) is both unclear and insufficient. Details of the specific drugs and doses in the standard treatment and Polypill arms of the trial should be given.

**Response:** We disagree with the reviewer’s comments. Substantial risk factor reductions were observed in the Polypill group. The problem was that the investigators gave the participants in the Standard Care arm aggressive risk factor treatment. It would be very difficult to draw any conclusion from the specification of the individual drugs and doses. The extent of this treatment was the critical factor—simply they gave enough medications to control the risk factors. In other words, the major issue is that highly educated and trained investigators at tertiary healthcare facilities did an excellent job reducing the risk factors in the Standard Care group. They did not fully appreciate or accept that the trial was conducted to determine the benefit of the Polypill in a research setting. The care offered is not, in our view, representative of the typical medical care in Sri Lanka.
Other essential Revisions

2. The authors regard the fact that the standard treatment group received drug treatment as unexpected. Few readers will regard this as unexpected, since individuals were selected according to having a 10 year CVD risk of 20% or greater, in whom drug treatment is recommended and generally offered to reduce cholesterol and blood pressure. Given that there is uncertainty any expected difference in risk factors reductions between the two arms it is questionable whether the primary objective of the study could ever have been achieved. Discussion on this is needed.

Response: Since Sri Lanka is a developing country, the aggressiveness of treating cardiovascular risk factors was not expected. However, conducting the study in tertiary care explains this aggressive treatment of risk factors, as mentioned in the manuscript.

3. The Polypill concept, proposed by Wald and Law, is to offer the Polypill to individuals not on the basis of risk factor measurements but to everyone over a given age regardless of risk factor measurements. A comparison of standard treatment in all with a CVD risk of 20% or greater versus Polypill for all 50 years of age and older (for example) would have been a better design that may have shown a difference in risk factor levels and provided useful information on acceptability. A discussion on this is needed.

Response: Our study was not designed to examine the Polypill as described by Wald and Law. Although giving the pill to everyone above 50 years old could be applied in developed countries, this approach may not be feasible in developing countries (the focus of this paper). In our view, to have a reasonable cost benefit ratio, limiting the Polypill to high risk group, at least initially, would be preferable.

4. The choice of a Polypill, which includes aspirin for use in primary prevention needs explanation. Aspirin is not generally used in primary prevention because of concern that the risks of life-threatening bleeding outweigh the benefits in people who have not had an ischaemic vascular event.

Response: There is disagreement in the scientific community regarding use of aspirin for primary prevention. We would agree with the reviewer, if our study population was at low risk for CVD. However, since our study population was at high risk for CVD, including aspirin in the Polypill seemed reasonable.

5. The adherence to treatment in each arm is not reported. How do the authors know that treatment was taken? Results on this should be given.

Response: Adherence in the polypill group was reported briefly on page 8. However, in response to the reviewer’s comment, we added more detailed information to the text.
6. The side-effects reported in each arm are not reported. These should be given on a symptom by symptom basis indicating which symptoms led to treatment being discontinued.

**Response:** We added a table that summarizes the major side effects (Table 3).

7. The authors conclude that doctors were "skeptical about not to monitor CVD risk factors (as suggested by Wald and Law)" (page 9). Based on what is reported in this paper, it seems that the authors may have misquoted Wald and Law’s recommendation on risk factor measurement. Wald and Law proposed that risk factor measurement should not be used to select individuals for treatment because the risk factor levels add little discrimination to age in predicting who will and will not suffer a future CVD event. This is not the same as "agreeing with Wald and Law on lack of need to monitor CVD risk factors" as stated in Table 4, which could relate to the measurement of risk factors after treatment has started to assess an individual’s response to treatment. Clarification on what question was asked and, indeed, whether the question was raised in the Wald and Law paper is needed.

**Response:** The reviewer’s comment is inconsistent with comment # 3 by Reviewer #1 which reads “….either not to monitor (as suggested by Wald and Law), or  “. The paper as well as the comment by Reviewer #1 implies “monitoring” not “screening”, as the reviewer mentioned.

8. The table describing the results of the questionnaire is not very informative. More detail is needed on the questions asked, the answers and the scoring system.

**Response:** We added more information on the questions to Table 4 (now Table 5)

9. In the Introduction, the authors state that the TIPS trial suggested that the overall benefit of the Polypill might be less than that predicted by Wald and Law (60% versus 80% risk reduction). The difference between the TIPS trial estimates and the Wald &Law predictions can be explained by the lower dose of simvastatin used in the TIPS trial (20mg rather than 40mg) together with non-adherence to treatment, as correspondence in the Lancet, following publication of the TIPS trial explained (The Lancet, Volume 374, Issue 9692, Page 781, 5 September 2009). This should be stated and referred to.

**Response:** We have included the reviewer’s comment (Page 4) and the citation (ref#6).
10. In the Abstract "Patients were recruited according to the pre-specified schedule". This needs to be clarified?

Response: This was clarified and the text now reads "Patients were recruited in a six-month period as planned."

Discretionary Revisions
There is no information on cost and resource use in each arm. One of the potential advantages the Polypill approach is simplicity and a reduced requirement for add-on treatment. Even though this trial design does not adopt the Polypill approach, there may have been differences in the extent to which resources were used, clinic visits, clinical staff time, and the costs of treatment. Some comments on cost would be helpful.

Response: This information was not collected.