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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Version: 5 Date: 1 November 2010

Author's response to reviews: see over
Ref# 4748862633961545

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 second revision meets your acceptance.

Sincerely,

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Reviewer: Matthew G Law

I'm happy with the authors response to my initial comments on this paper. They pretty much fully accepted and addressed my points. The only slight caveat is my point 3, about further discussion on the design of a polypill trial in a developing country. They did add some brief discussion, but I thought this was pretty weak. However, I'm happy to leave whether this is sufficient as an editorial decision.

Response:
No action required

Reviewer: David Wald

Major Revisions
1. The fundamental problem is that it is not possible to achieve the primary objectives of the trial ie. to determine “the reduction in systolic blood pressure, total cholesterol and estimated 10-year CVD risk from the Polypill” because the control group received similar treatment to the Polypill group. In this respect the trial failed and the authors should come clean on this.

Response:
We agree with the reviewer’s comments. In the revised manuscript, we have been more explicit in mentioning that the trial failed to document the anticipated benefits of the Polypill (Conclusions, pages 3 and 12)

2. The authors acknowledge that the control group received more treatment than expected but do not seem to accept that this makes it impossible to get an unbiased estimate of the risk factor reductions or decline in risk. Instead they ignore the randomised design and report the “before and after” BP, Cholesterol and CVD risk change in each arm of the trial (Table 4), concluding that the Polypill achieved “marked reductions in risk factors”. This may be true but one cannot quantify the effect because the results are biased – the reductions will have been overestimated due to “regression to the mean” since the patients were selected as having high levels at the start. The 74% reduction in risk observed on the Polypill, for example, (Table 4) will also be an over-estimate and this is not discussed. Also, no attempt is made to allow for regression to the mean effect.

Response:
We agree with the reviewer that “regression to the mean” could partially explain the marked reductions in risk factors. In the revised manuscript, we have included this comment (Page 11, 12). However, we disagree with the reviewer’s comment that we ignored the randomized design. Table 4 shows the results by treatment groups comparing the changes in the Polypill group versus the Standard Practice group.
3. It seems that “Polypill” and “standard Care” treatment must have been similar (because BP and cholesterol changes were similar), but were they? It appears that treatment details are not available (is that correct? – the comment on page 11 is limited to doses). Assuming that the treatments were similar then the result is that the Polypill can achieve as good risk factor reductions as using separate components with less fuss and individual adjustments of drugs and doses.

Response:
As we mentioned in page 11, regardless of the details of treatment prescribed, which would be of limited value here, the use of non-study drugs defeated the objective of the trial by making it difficult to observe the expected treatment effect of the Polypill. In the revised version, we have incorporated the Reviewer’s comment that the simple Polypill that requires fewer alterations of treatment was as effective as Standard Practice, which highlights its potential usefulness in prevention of CVD (Page 12).

4. Monitoring - Wald and Law, in their 2003 paper did not proscribe monitoring, they stated that there was no need for routine monitoring (intervention is effective whatever the initial levels of the risk factors and with combination treatment is robust to variation in person-specific drug effects) and that there were advantages in avoiding monitoring (random fluctuations in BP and cholesterol within individuals tend to mask the changes between individuals in the systematic effects of the interventions leading to false indications of large or small effects of treatment). If a question on monitoring is put to Physicians it should present the whole argument, not bits of it, as is the case in Table 5 of this manuscript. The question should then ask whether Physicians agreed that there was no need for monitoring instead of asking “How do you rate your agreement on not to monitor risk factors.”

It may be best to omit this question and the results from it.

Response:
As mentioned in page 6 (Methods section), Wald and Law paper was mailed with the questionnaire to the physicians which should have resolved any misunderstanding of the wording of the question. Further, rather than getting a yes/no answer, we wanted to get a graded degree of agreement, which was the reason to use the question format we used.

5. Conclusions:
(i) Lessons from this kind of study design – RCT not valid when people are told they are at high risk because control groups will end up taking treatment
(ii) BP, cholesterol and CVD risk reductions comparing pre-treatment and post treatment are as described in Table 4, but the true estimates are uncertain and will be lower due to regression to the mean
(iii) High acceptability of Polypill
(iv) Polypill simpler and less need to alter treatment
Response:
We have incorporated these suggested conclusions in the revised manuscript (Page 12).

6. The paper, in my view, needs further revision on scientific grounds. The above comments may help the authors revise the paper.

Response:
We thank the reviewer for his very helpful comments and suggestions.