Author's response to reviews

Title: An explanatory randomised controlled trial of a nurse-led, consultation-based intervention to support patients with adherence to medication taking for type 2 diabetes

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Author's response to reviews: see over
This article regards a pilot/explanatory study of a nurse-led intervention to facilitate type 2 diabetes patients’ medication adherence. The underlying hypothesis is that lack of motivation and ‘simple’ forgetting both result in non-optimal adherence. This hypothesis is challenged during a nurse-led consultation by elicitation of patient’s personal beliefs.

Major compulsory revisions.

1. Only the glucose lowering medication was taken into account. This is a considerable curtailing of the outcome. Both in the Title and the Discussion section the authors should insert ‘glucose lowering’.

   We have added the words “glucose lowering” to the title and to the discussion section.

2. Participants will have taken one, two or three oral glucose lowering medications. Some will have taken two oral medications and insulin. Were people on insulin excluded? This is an important issue! Please mention.

   People on insulin were not excluded as long as they were also taking oral glucose lowering medication. We have added a sentence to make explicit that using insulin was not an exclusion criteria.

3. How as the primary outcome measured in the standard care group? As far as I understand also the patients from the standard care received the TrackCap devices. In fact they should for methodological reasons. However, this is not described in the Study Procedures section.

   We have clarified these details in the study procedures to make it clear that the initial allocation to TrackCap and standard packaging was only prior to the intervention visit, and that after the intervention visit all participants used a TrackCap.

4. In the results section the authors do not mention whether the nurses succeeded in providing one patient the intervention and may be the consecutive patient the standard care.

   We have clarified the section in procedures to describe how telephone randomization was carried out in advance of the patient visit and that nurses then allocated their behaviour in the visit according to the randomization.

5. In the Discussion section the authors state the positive response rate of 34% is ‘comparatively high’. What is this statement based upon? I think they are too optimistic about the external validity of their results.

   Concerns about external generalizability of the results of randomized trials are of particular concern when only a small proportion of those potentially eligible for an intervention are recruited to the trial. A survey of three primary care journals by Jones and colleagues found recruitment varied between 16 and 70%, *BMC Family Practice* 2009, 10:5) and we have also identified a systematic review by Wens and colleagues in which some of the trials report equivalent participation rates, although it is by no means clear that their procedures for...
identifying a sampling frame were as rigorous as those we used. We have therefore rephrased the description to make this clear. We also collected anonymised information about the wider population from which the participants were drawn, so although there are likely to be unmeasured factors that might influence response to the intervention, we were able to show a broad similarity: “we obtained an acceptable rate of participation from eligible patients, and were able to demonstrate that the characteristics of these individuals were similar to the wider population from which they were recruited”.

6. The Discussion could be more critical. It should address the response rate (people with comorbidities excluded!), the discrepancy between outcome measures, contamination (why not randomisation by practice?), the very short follow-up, the restriction to glucose lowering medication. The discrepancy between the MARS outcomes and the outcomes as measured by the TrackCap is striking and points to the validity of both measures.

We have included all these issues in a new paragraph in the discussion section.

Minor essential revisions

1. The intervention consisted of two components. In the design section it remains unclear (even from the patient flow diagram) whether the authors mean that ‘motivation’ and ‘action planning’ are the two components, or that another trial regarding the impact of electronic medication measurement was the first part of the intervention. The description of the intervention on page 6 clarifies this issue. Please rewrite the first part of the design section on page 5.

As requested we have rewritten this section to try and make the two issues noted here clear. We have done this by describing the trial as carried out in weeks 9 to 20 of a larger study rather than running concurrently, which we agree is inaccurate.

2. A literature reference about the medication measurement ‘which is reported elsewhere’ is lacking on page 5.

Reviewer 3 also raises this point. This report has not yet been published and we suggest that removing this phrase would be appropriate. The results of the medication measurement study are reported in the results already, and we have added to the discussion to highlight this and emphasise its importance.

Discretionary Revisions
1. The article is well written and describes the short-term efficacy of the intervention. It also wants ' to inform sample size and other parameters....' This part of the sentence will not be clear to the readership. Please define more clearly.

We have revised this sentence to emphasize the issue of sample size. The other parameters referred to are principally the study design, optimizing intervention and control groups by identifying those components most likely to have led to an effect.

2. Is the device described anywhere or is it validated? Yes, but I read it in the Discussion section. Please describe in the Methods section.

We have added the details of the validation to the methods section.

3. The measures are fully described in the trial protocol. However, for the purpose of this article I would prefer a short description of the Medication Adherence Report Scale.

We have added a short description of this measure.

4. In general, the intervention is described well. I would suggest to exchange the second and third paragraphs, i.e. start with the description of the training, the protocols etcetera. Indeed, contamination is a major issue.

We have followed this helpful suggestion.

5. Abstract: primary outcome available for 194 or 195 patients? The intervention regarded a single session. However, please add: of 30 minutes

There was a primary outcome available for 194 participants as stated in the abstract. This number is consistent with the data given in Table 4. The phrase "30 minutes" has been added.

Reviewer: Justin Beilby

Reviewer's report:

Review

My comments have been linked to Headings but are all Minor Essential Revisions.

An explanatory randomised control trial of nurse-led consultation based intervention (Farmer et al).

ABSTRACT:

The abstract is appropriate for the paper and provides the summary of the findings as per expected. I note the comment re the need for an important longer term study to assess clinical and cost-effectiveness outcomes. I would prefer they add over "a longer period of time" in this abstract. I think it is a key point for future studies.

We have added the suggested phrase.

BACKGROUND

I have no comments on the background except to note the importance around looking at medication adherence and relying on self report. The other point around self adherence is the length of

We have added a brief phrase to highlight the issue of the length of the intervention: "Both components are delivered in a single, brief intervention, although, if effective, future work could
time the intervention is used. I think this should be discussed as part of the introduction.

**METHODS**

The method are well defined and the intervention model outline. The randomisation model is noted and primary care setting in 13 general practices. In describing the intervention I like the information around the time the nurses were involved with the patients and more importantly the time required to do the training. One of the issues around this type of intervention is the cost effectiveness required in a larger study. I note the intervention for the clinic nurse across the 13 practices lasted approximately 30 minutes and data collection 20 minutes. Is there any other studies that have looked at the time for training and intervention in the area of medication adherence?

We are not aware of any such studies looking at costs in medication adherence studies. Most health economic evaluations in this area have been conjoint analyses. The 2009 NICE guideline on adherence did not identify any cost-effectiveness analyses.

**RESULTS**

We agree that Figure 2 has potential to be confusing and does not add much to the paper and we agree that it should not be included in the paper.

The mean difference between the groups in the percentage of days of correct number of doses taken was 8.4% with the P-value of 0.044. This improvement is illustrated in Figure 2 and I am not totally convinced re thus figure should remain or at least “lines of best fit”/trend added. Figure 2 does outline the sustained effect really began from day fourteen as I understand the graph, although this will need further information for the reader to follow.

There were no significant differences for secondary outcomes. Importantly the authors comment in the results the intervention may have been larger for those with better glycaemia control, older age and higher self adherence at baseline. I note the mean total of time difference between the intervention group of 74 minutes versus 42 minutes is 31 minutes. An intervention facilitator spent an average of 2.3 hours per patient listening to tape recordings compared to 1.2 hours in standard care. This time required to deliver the intervention needs further discussion in the final version of the paper...These are significant time imposts in a busy GP practice.

We have added further discussion acknowledging that this intervention requires further simplification of the delivery and quality assurance methods before it is more widely used. However, it should be noted that the detailed review of tape recorded interventions is a feature of the explanatory design of the trial and would not be replicated in a pragmatic trial or in clinical practice.
## DISCUSSION

The authors make the valid point that the study effect was over 12 weeks and there is no doubt we need longer studies. Follow up to look at the true effect of adherence and whether a one off affect and the sustainability can be clarified. The only other comment is the need for a larger study to look at both cost effectiveness and clinical outcomes. The time required to train nurses to complete this intervention and then involve the patients is substantial and it maybe useful to spend a little bit of time discussing how to create the sustainability of this in a broader practice based intervention. This is probably the key point that is missing with the discussion. In summary this is a useful explanatory study that is well constructed and implemented.

We have also added a brief discussion of the importance of developing an intervention that is sustainable to the discussion: “The intervention used in this study was delivered on a single occasion to identify the impact of the volitional and motivational components, however, in a larger study the intervention would need further development to ensure that the effect was sustained”, and if the action planning component was effective alone it would be much shorter to deliver. Other factors relating to sustainability include the provision of initial training (we trained nurses for one day, of which about half was intervention delivery training and half related to trial issues).

**Reviewer:** Hilary Hearnshaw

**Reviewer's report:**

1. The study is well justified, well conducted and well reported. This study would have required a great deal of effort in organising, recruiting and gathering data. It should be published.

2. The results are clearly presented, though it could be made clearer exactly what Figure 2 is telling the reader. Reviewer 2 has suggested that this figure is removed. We have discussed and agree that it does not helpfully contribute to reporting the study results or interpreting the findings and would agree it should be removed.

3. The discussion addresses the main findings, the limitations and the relevance of the findings to clinical care. I have a couple of queries, though, which lead to discretionary revisions.

4. Is this an explanatory RCT (Background paragraph 5 and Discussion paragraph 6) or an exploratory one? If explanatory, what exactly has been explained? In the Discussion paragraph 6 it is stated the aim was to estimate the effect of the intervention (presumably its effectiveness), but in the Abstract/Background and Background paragraph 5 it is the efficacy which is mentioned. Which is it? We designed this trial (as laid out in the protocol paper) as an explanatory study with the aim of establishing efficacy of the proposed intervention. The term “effect” was intended to be “efficacy”.

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5. In Methods, Trial design, it is mentioned that the study on electronic medication measurement is reported elsewhere, but no citation is given. I do not really understand how that study and this study complement each other, and feel more description of that should be given. The protocol was published in 2008 (reference 10) but not the full study. It is not clear how much was presented at the ADA in 2009. When was the study conducted? We are told the pilot was in 2001 (Analysis methods paragraph 1). It leaves me wondering just how and when it all fits together and whether I am being told the full story. I would not wish other readers similarly to feel any suspicions of the reporting which might make them devalue the findings. The result is important.

The study described as a “pilot” was an evaluation of the use of electronic medication measurement in a cohort of people with diabetes in a single UK general practice. Subsequent work funded by UK Diabetes in 2002/3 involved questionnaire development. The design of the study described in this report was developed between 2004 and 2006 and was funded by the Medical Research Council in 2006. The trial was completed in 2008 and the primary results of the efficacy study were reported at the American Diabetes Association Meeting that year. The first reviewer has asked for a clearer explanation of the relationship between the study of efficacy of the intervention, and the study assessing impact of medication monitoring. We have done this and hope it now gives a clear explanation of the relationship of the two studies.

The report of the study assessing impact of medication monitoring is currently being finalized, so we agree that it is inappropriate to say it is reported elsewhere. However, this paper does present the results in Table 4 (prior randomization to medication monitoring device). We have drawn attention to this in the results section and have added a comment in the discussion in the absence of a published report.