Author’s response to reviews

Title: Effectiveness of medicines review with web-based pharmaceutical treatment algorithms in reducing potentially inappropriate prescribing in older people in primary care: a cluster randomized trial (OPTI-SCRIPT study protocol)

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Author’s response to reviews: see over
Dear Editors,
Thank you for the further helpful comments and suggestions received. We found the suggestions very helpful and hope we have addressed any outstanding concerns raised. We have submitted a revised version of the protocol with changes marked in red so that the exact revisions made can be seen.

We outline the specific responses to each comment as follows:

**Response to comments from BMC manuscript peer review**

- The authors do not agree that the intervention is not particularly complex and provide, in my mind, unnecessary strong arguments that they are correct. Fair enough, but there is no need to emphasize the complexity and not really any need to define academic detailing in the text. Obviously, as the authors state themselves (“a short educational presentation about PIP as a concept”) is the qualification component to call it academic detailing, and I think it is quite obvious that this is not a very strong component of the intervention. However, that can be accepted. It is more difficult to accept what is presented as one of the other components of the ‘intervention’. The authors claim that “Medicines Review” is one such component, but that is in fact an intermediate outcome of the intervention. The main aim of the “academic detailing” is to give the GPs motivation and tools to perform medicines reviews on a number of specified patients. We don’t know whether the GPs will do this or not, and if they do it, whether they will follow the suggested protocol by using the web-based algorithm or do it in some other way. So, as I see it, the intervention comprises the following components: a) practice visit by pharmacist for education on PIP and on how to conduct a medicines review, plus demonstration of the web-based algorithm and how to use it; b) making the web-based algorithm available for the GPs for the selected patients, with detailed feedback on PIPs including treatment recommendations; c) individually developed information leaflet for the patients.

*Author response*
We have removed the definition of academic detailing from the text. In terms of the medicines review, we would argue that this is the central component of the intervention as its completion, for this study, can only take place using the web-based algorithm. The GP will have to log onto this and go through each step in order to submit their review outcome form, therefore, if we have the review outcome, we can be sure the practice has used the web-based algorithm and delivered the medicines review intervention as planned. The outcome is then
regarded as the changes made in the patients’ prescription following this review. We will also be tracking prescribing changes throughout the intervention period which will enhance the process evaluation of the study and ensure we capture all activity potentially related to this intervention even if the specific web-based intervention is not done. We accept the suggestion that the intervention can be described as 3 main elements and have clarified the intervention as follows on:

Page 2 (abstract): “Practices will be allocated using minimization to intervention or control arms, with intervention participants receiving a complex multi-faceted intervention incorporating academic detailing, medicines review with web-based pharmaceutical treatment algorithms that provide recommended alternative treatment options, and tailored patient information leaflets.”

Page 4 (aims): “The intervention combines academic detailing, medicines review with web-based pharmaceutical treatment algorithms that provide recommended alternative treatment options, and tailored patient information leaflets.”

Page 7 & 8 (intervention): “The intervention consists of academic detailing, medicines review with web-based pharmaceutical treatment algorithms and tailored patient information leaflets. The academic detailing will involve a research pharmacist visiting intervention GPs in their own practices. As part of that visit, there will be a short educational presentation about PIP as a concept, the criteria used to measure it and a summary of studies conducted in Irish primary care on the topic as knowledge of PIP may be a barrier to appropriate prescribing in older patients. [1] Subsequent to this, practices will be asked to complete 10 medicines reviews within a 6-8 week period, with a reminder issued if they are not completed within that time frame. An extended time-frame may be negotiated, should a practice require it. During the medicines review, the GPs will use web-based treatment algorithms specifically designed for this study and accessible using a link and designated password. The algorithm will guide the process from the GP perspective, and does not incorporate patient involvement. It is a page-by-page structure, which will be completed when the GP fills in a review outcome form, detailing decisions made by the GP and patient together, including the reasons for maintaining a PIP, which is a key element of this study. Once the review outcome form has been filled in, the medicines review is complete.

The medicines review will take place in the GP practice and will be scheduled at a date and time that is convenient to both the GP and the patient. In group practices where more than one GP is participating, the reviews may be divided between them in a manner that is most suitable to the practice workload. The pilot study indicated that the preparation for the review may be more time consuming for the GP than usual but there was no indication that the consultation itself would be significantly longer. These components are presented in Table 1.
### Table 1: Intervention components

<table>
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<tr>
<th>Intervention component</th>
<th>Description</th>
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| Academic detailing     | A research pharmacist will visit the intervention practices. During the academic detailing, the pharmacist will:  
  - Discuss the concept of PIP with the GPs, focusing on the prevalence and consequences of PIP in primary care  
  - Discuss the pharmaceutical treatment algorithm  
  - Discuss the medicines review process  
  - Demonstrate the web-based platform for accessing the pharmaceutical treatment algorithm for use in a medicines review with each participant patient |
| Medicines review with web-based pharmaceutical treatment algorithms | GPs will be asked to:  
  - Schedule a medicines review for the patients next appointment  
  - Log-on to the designated website using individualised user-names and passwords  
  - Access the individualised web-based pharmaceutical treatment algorithms during the medicines review  
  - Conduct a medicines review with each patient following the page-by-page web-based pharmaceutical treatment algorithms. Each pharmaceutical treatment algorithm has the following structure:  
    - Section A: The individual PIP with reason for concern  
    - Section B: Alternative pharmacological and non-pharmacological treatment options  
    - Section C: Background information (where relevant)  
  - Complete the process by submitting the review outcome form for each PIP per patient  
Each GP will also be provided with a full, paper based compendium of pharmaceutical treatment algorithms for reference. |
| Patient information leaflets | For every alternative therapy option, a brief patient information leaflet has been written. These leaflets describe the PIP and the reasons as to why it may be inappropriate. They also outline the alternative therapies the GP may offer instead. |

*Note: The decision on whether to follow the recommended treatment alternatives will be at the discretion of the GP, weighing up the risks and benefits and patient preference.*

- The authors have not responded to my suggestion to declare the type of intervention in the title. This should be reconsidered. The term ‘a complex intervention’ does not give any information about the kind of intervention, regardless whether we agree on the complexity or not. The reader wants to know the type of intervention under investigation, not that it is something anonymously complex. It is more informative to see words like “medicines review” or “treatment algorithm” or similar in the title than “potentially inappropriate prescribing”. Why not build on the initial title and, for example, write: Optimizing prescribing for older people in primary care through practice-based medicines reviews: a cluster randomised trial (OPTI-SCRIPT study protocol), or Effectiveness of medicines review with web-based treatment algorithms to reduce inappropriate prescribing (optional: for older people) in primary care: a cluster randomised trial (OPTI-SCRIPT study protocol), or something similar. Whatever the choice, the title should not start with the type of study.*
In line with my reasoning above the need to revise the aims remains. First, the initial part about conducting a cluster RCT should be deleted. This refers to the method of study to respond to the aim, and is not an aim in itself. So the real aim starts with “... to determine the effectiveness and acceptability of a complex, multi-faceted intervention ...”. In this part, ‘medicines review’ is mentioned, and this has to be modified as commented above.

The aim of this study is to determine the effectiveness and acceptability of a complex, multi-faceted intervention in reducing the level of PIP in primary care. The intervention combines academic detailing, medicines review with web-based pharmaceutical treatment algorithms that provide recommended alternative treatment options, and tailored patient information leaflets. The intervention development was informed by the Medical Research Council (MRC) guidelines for the development and evaluation of randomized controlled trials (RCTs). It was piloted with a group of five GPs and found to be feasible and acceptable within this group.

It is now clearer, but still not totally clear how the GPs will be recruited. The authors write (Methods, Recruitment and allocation, 1st paragraph): “All eligible practices will be invited to participate ...” and “When a GP agrees to participate, they (or the practice nurse/secretary) will be asked to identify a random sample of 50 patients ...”. So practices are invited, but individual GPs agree? And then someone (?) selects a random sample of 50 patients. It is also stated in the first section of Methods (Trial design) that “... participation will be defined as attendance at the academic detailing visit and undertaking a medicines review.”

a. Is it correct that participation is exclusively decided by an individual GP or can participation be decided at group level by one person representing all GPs in a group practice?
intervention arm and as providing patient prescription data in the control group. Practices that do not meet these criteria will be considered lost to follow-up (see Figure 1).”

b. How will the random selection of 50 patients take place? Will it take place for each of the GPs that have accepted participation, or will the patients for all accepting GPs be combined to one group before the random selection. In the first scenario: how will the 50 patients be distributed among, for example, three participating GPs? Dependent on number of listed patients?

Author response
This is a pragmatic RCT, the proposed intervention is modeled in such a way that it could be incorporated into usual clinical practice, if proven to be effective. General practices share patient lists amongst individual GP partners, no personal GP lists operate amongst participating practices.

We have clarified this as follows on page 6/7:
“All eligible practices will be invited to participate by email (or letter where email address is unavailable), which includes a study information leaflet, outlining steps of the intervention and availability of Continuing Medical Education (CME) points for participation. When a practice agrees to participate, a member of staff (e.g. a GP, the practice nurse/manager) will be selected by the practice. The research team will instruct the designated person on how to identify a random sample of 50 patients aged 70 years and over from the patients of participating GPs within the practice. They will pseudo-anonymise the records by assigning the patients a study ID and send a copy of the pseudo-anonymised prescription records to the research team where a research pharmacist will generate a list of potentially eligible patients i.e. patients with PIP.”

In the second scenario: what will happen if three GPs have accepted but the selected ten patients are listed on two of the GPs?

We have clarified this as follows on page 8:
“The medicines review will take place in the GP practice and will be scheduled at a date and time that is convenient to both the GP and the patient. In group practices where more than one GP is participating, the reviews may be divided between them in a manner that is most suitable to the practice workload.”

c. What will happen if a GP has accepted to participate, but does not show up for the visit by the pharmacist or does not perform any medicines review?

Author response
The pharmacist will conduct the academic detailing in the practice. The visit will be scheduled at a date and time that is suitable to the participating practice. Should a practice decide to not participate in the academic detailing and or fail to conduct the medicines reviews, the practice will be excluded from the study.
These practices will fall into the category of ‘Lost to follow-up’, as outlined in Figure 1 Flow of practices and patients through RCT and recorded as such.

We have clarified this as follows on page 5:
“We will keep a record of participating GPs and participation will be defined as attendance at the academic detailing visit and undertaking medicines reviews in the intervention arm and as providing baseline data in the control group. Practices that do not meet these criteria will be considered lost to follow-up (see Figure 1).

• The authors confirm that they have not assumed any change in the control practices. However, their arguments are not fully convincing for two reasons: a) In this study the control GPs will receive feedback on PIP for only ten patients per practice. In my assessment this is a more specific intervention than what the authors refer to as “less intensive feedback”. Therefore, I still think it is more likely than not, that some of these GPs will be motivated to change their prescribing towards less PIP; b) The authors reference to Cochrane reviews on audit and feedback is relevant, but it should be remembered that this is not evidence that changes may not occur for other reasons. It is also not uncommon that one reason for no intervention effect is that the control arm has also changed in the intended direction. When conducting RCTs, it is mostly recommended to rather be on the safer side, which in this case would mean to assume a slight improvement in the control arm as well.

**Author response**
Feedback can be effective in improving professional practice and the effects are generally small to moderate. Feedback is more likely to be effective when provided intensively. We consider the feedback in the control intervention (usual care with simple feedback) not to be intensive as it is only provided once, the information it contains is limited to the patient ID number and the medication class to which the inappropriate prescription belongs. It does not specify the exact issue and does not offer actionable recommendations. We do not expect the GPs in the control group to act on the information they receive, based on our previous experience of conducting pragmatic RCTs in Irish general practice. However, we do accept that it is possible that they will do so and we will monitor for this. If this happens, it would reduce the effect size of the intervention. However, we don’t think we can predict the potential size of this effect. We have proposed to deal with this by including the national control sample who will not have received any study related information or feedback. The current proposed sample size falls within the resources available for this study. Further inflation of the sample size would threaten the study’s feasibility. We believe this is a pragmatic exploratory type trial and that it will provide evidence to guide further trials that will be needed to confirm any potential effect or modify future interventions.

We have clarified this as follows on page 8:
“Data for patients in the control group will be reviewed during recruitment and a personalised patient list for the 10 recruited patients will be fed back to the GP. This list will summarise the medication class to which the individual patient potentially inappropriate medication belongs, not the specific PIP and will not provide actionable recommendations for change. Participants will not receive an academic detailing visit and will not be prompted to carry out a medicines review with the individual patients and will not have access to the pharmaceutical treatment algorithms with alternative therapy options.”

- It is good that the study will include an evaluation of reasons for any detected impact on the performance of the control group, although “brief telephone interviews” may not be the most appropriate assessment method. Some more comments on this potential weakness of the study should be added.

**Author response**
We have clarified this as follows on page 15:

“...with a maximum of 10 patients per cluster and factoring in a loss to follow up of 10%, a total of 22 GP practices and 212 patients per arm will be required."

“...with a maximum of 10 patients per cluster and factoring in a loss to follow up of 10%, a total of 14 GP practices and 132 patients per arm will be required.

- It is not quite clear how the final sample size has been decided on the basis of the two separate calculations, which resulted in 22 practices and 106 patients per arm, and 14 practices and 66 patients per arm, respectively. It is stated (Sample size, last sentence) that “… at least 22 practices and 220 patients will be required for this study.” In the Abstract it is also stated that “This study” will involve “22 practices (clusters) and 220 patients”. Two questions must be answered:

  a. Isn’t it correct that the total sample should be 22 practices in each arm?

**Author response**
This has been clarified as follows on page 12:

“...with a maximum of 10 patients per cluster and factoring in a loss to follow up of 10%, a total of 22 GP practices and 212 patients per arm will be required.”

b. How was the reasoning behind deciding on 220 patients (=10 patients per practice), when the first calculation indicated 106 patients and the second calculation indicated 66 patients?
Author response
This has been clarified as follows on page 13:
“These calculations indicate that we would need at least 22 practices and 212 patients to detect a difference between the intervention and control arms for both of our primary outcome measures. On the basis of these calculations, we aim to recruit at least 22 practices, with 10 patients per practice, giving a total of 220 patients. With this sample size, we would have at least 80% power to demonstrate a 10% absolute reduction in the proportion of PIP and a 30% relative reduction in the mean number of PIPs.”

• As mentioned above, the authors should modify the description of the components of the intervention.

Author response
Please see previous response on pages 1 and 2.

• The authors state in their response (and on page 13) that “The academic detailing will demonstrate the process of the medicines review with the intervention practices but the research team will not monitor how the GP implements the study protocol after this”. However, already on page 8 it has been stated that “…practices will be asked to complete 10 medicines reviews within a 6-8 week period, with a reminder if they are not completed within that time frame.” To me, these two statements are not fully compatible. It is further not clear what will happen if the reviews are not completed within the time frame. Will there be further reminders? Extended time frame?

Author response
We have clarified this as follows on page 13:
“The academic detailing will demonstrate the process of the medicines review with the intervention practices but the research team will not monitor how the GP implements the study protocol after this, other than to remind the practices to complete the process within the allotted time frame.

And on page 8:
“Subsequent to this, practices will be asked to complete 10 medicines reviews within a 6-8 week period, with a reminder issued if they are not completed within that time frame. An extended time-frame may be negotiated, should a practice require it.

• There are still errors, like missing words, e.g., in Discussion, limitations (p. 17), fourth and sixth sentences; as well as in Table 1, third section, third line. There are also errors in Table 2 like: no space between words or incorrect space; no capital letter at start of entry; truncated word.

Author response
These errors have been corrected as recommended.
Tables should start on a new page.

Author response
This has been corrected as suggested.

The reference list is now almost free from editorial errors.

1) Ref #1: Full stop after title.
Author response
This reference has been corrected as recommended.

2) Ref #9 and 10: No space before and after hyphen.
Author response
These references have been corrected as recommended.

3) Ref #14: Semicolon after publisher.
Author response
This reference has been corrected as recommended.

4) Ref #16: Add all authors up to 30.
Author response
This reference has been corrected as recommended.

5) Ref #26: Colon before page numbers; page numbers shown as II-2 – II-45, or II 2-45.
Author response
This reference has been corrected as recommended.

6) Ref #27: Citation is not complete (see the article for required style; cf. #29!).
Author response
This reference has been corrected as recommended.

7) Ref #48: Are page numbers available?
Author response
No page numbers are available for this reference, hyperlink added.

References: