Author’s response to reviews

Title: A cluster randomized controlled trial to determine the effectiveness of a complex intervention in reducing potentially inappropriate prescribing in primary care: OPTI-SCRIPT study protocol

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Author’s response to reviews: see over
Dear Editors,

Thank you very much for the helpful comments and suggestions received from the editorial team and peer reviewer. We found the suggestions very helpful and hope we have addressed any concerns raised. We have submitted a revised version of the protocol with track changes 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**

- In my judgement this algorithm and the recommendations for its use are the main intervention components that will be tested. The visit by the pharmacist in each practice at the start of the study seems mainly to focus on demonstrating the algorithm and give instructions how the medication review process should be undertaken, and are therefore not examples of academic detailing. An additional part of the intervention is that patients will be provided with tailored information leaflets.

**Author response**

O’Brien et al, define educational outreach visits (EOV’s) or academic detailing as “use of a trained person from outside the practice setting who meets with healthcare professionals in their practice settings to provide information with the intent of changing their performance. The information given may include feedback about their performance. The intervention may be tailored based upon previously identified barriers to change”.[1]

In this study, a research pharmacist will visit the GPs in the intervention arm in their own practices to provide information with the intent of changing their performance, i.e. potentially inappropriate prescribing (PIP). 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. This will address GP knowledge of PIP, as many primary care doctors possess a poor knowledge of PIP and prescribing guidelines such as the Beers criteria, which may be a barrier to appropriate prescribing in older patients.[2]

We feel that this process does meet the definition of academic detailing, as outlined by O’Brien et al. [1]

We have clarified this as follows on page 8:

“The intervention consists of academic detailing, a medicines review, treatment algorithms for use during the medicines review and tailored patient information leaflets. Academic detailing can be defined as the use of a trained person from...
outside the practice setting who meets with healthcare professionals in their practice settings to provide information with the intent of changing their performance. [1] In this study, 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. [2] 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. 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. 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. 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. However, it does record decisions made by the GP and patient together, including the reasons for maintaining a PIP, which is a key element of this study. The components are presented in more detail in Table 1."

• The title is very broad.

*Author response*
We have clarified this as follows on page 1:
“A cluster randomized controlled trial to determine the effectiveness of a complex intervention in reducing potentially inappropriate prescribing in primary care: OPTI-SCRIPT study protocol”

• The aims should be revised. In my assessment the authors have not shown that this is a particularly complex intervention for the participating GP. He or she will get access to a web-based algorithm to be used for medication reviews of preselected patients. Alternative treatment options will be available and the GP has just to decide, in agreement with the patient, to follow these or not.

*Author response*
Complex interventions are “built up from a number of components, which may act both independently and interdependently.”[3] We feel that this intervention is a complex intervention as it has a number of a number of components, which may act both independently and interdependently. The components are:

1. Academic detailing (we have outlined above the reasons we feel this component meets the criteria for academic detailing)
2. Medicines Review
3. Web-based pharmaceutical treatment algorithms
4. Patient Information Leaflets.

Therefore, we feel the aims remain valid.
• The main issue that must be clarified is what is meant by “practices” and what is meant by “GP”. It seems on the one hand clear that practices are the unit of randomisation, not specifying whether they are solo practices or group practices. This would mean that the ten patients that will be recruited per practice could be managed by more than one GP. However, on the other hand, it is somewhat ambiguously mentioned that outcome forms will be “… completed by GPs at the end of each of the 10 medication reviews they conduct for the 10 recruited patients”, and further that the evaluation interviews with GPs “… will be completed within one month of them completing all 10 medicines reviews”.

Author response
GP participation in group practices may vary depending on the type of practice. In some practices GPs operate independent lists and in others a more team based approach is taken. As this is a pragmatic trial we are seeking to test an intervention that can be delivered across a range of practice types.

We have clarified this as follows on page 5/6:
“The trial will be conducted in primary care with GP practices as the unit of randomization. A practice can be a single-handed GP or can comprise of two or more GPs (group practices), however, not all GPs in group practices may wish to participate. We will keep a record of participating GPs and participation will be defined as attendance at the academic detailing visit and undertaking medicines reviews.

We have clarified this as follows on page 11:
“Process measure data for the intervention group will be collected by outcome forms completed by GPs at the end of each of the 10 medicines reviews they conduct for the 10 recruited patients. In single-handed practices, the same GP will conduct the reviews and complete the outcome forms. In group practices, where more than one GP is participating in the study, the reviews may either be conducted by an individual GP nominated by the practice or may be conducted between the GPs, with each GP completing the outcome form for the patient they reviewed.”

We have clarified this as follows on page 15:
“For GPs, the interviews will be conducted within one month of them completing their assigned medicines reviews i.e., for single-handed practices after all ten reviews and after completion of assigned reviews in group practices.”

• Another issue that should be clarified is the number of patients that will be on the lists received by the “control group GPs”. Will it be ten patients per practice as I understand is the case for the intervention practices, or will it in both arms be all patients with PIPs from the list of 50 patients provided by each practice for the baseline

Author response
We have clarified this as follows on page 9:
“Data for patients in the control group will be reviewed during recruitment and a personalised patient list, summarising the PIPS for the 10 recruited patients, will be fed back to the GP”.

- The first primary outcome is the “Proportion of patients with PIP”, but this outcome is not quite clear to me. Is it at all related to “level of PIP in primary care”. First, proportion of what? Of the ten patients recruited per practice?

Author response
We have clarified this as follows on pages 2, 10, 12:
“Proportion of participant patients with PIP”

- Second, if assuming that it means the proportion of the ten patients (and bearing in mind that all these ten patients have at least one PIP at the start of the intervention), a possible result could be that there is a substantial reduction of all PIPs among these ten patients but all of them still have at least one PIP. So the effect of the intervention would then be no change for the primary outcome.

Author response
We agree and this is the reason why we have also based the sample size calculation on a second primary outcome, the mean number of PIP per participating patient, as listed in Table 2.

- The authors have used this outcome for one of the sample size calculations, and by doing so they have chosen the scenario, that may give the lowest numbers of participants required for the assumed ten percent absolute reduction, given that their assumption for the calculations seems to be that there is no change in the control arm. However, this latter assumption is only valid if there is no change in the control arm. This has not been stated in the text, but must be clarified and commented.

Author response
This is a very reasonable query and we considered this during the development and planning of this study. Existing evidence suggests that provision of feedback alone does not change prescribing behaviour but it is possible that a control arm GP could use the feedback information to change the prescription. However, they will do this without any algorithm or support to suggest alternatives and would have to carry out a specific medicines review, which are not a routine feature of Irish general practice. We will keep a careful record of all the changes made in both the intervention and control practices to enable a full process evaluation of the study. In addition we have added the following text to the end of the sample size calculation section on page 13:
“Based on existing evidence that suggests simple, less intensive feedback does not alter prescribing behaviour [4-5], we have not anticipated an improvement in the control arm. However, we will monitor for this in the parallel process evaluation.”
We have also added the following to the end of the qualitative process evaluation section on page 16:

“In addition, as part of the process evaluation we will conduct brief telephone interviews with the control group GPs to ascertain any potential impact of the feedback they receive based on the baseline data.”

- The same relates to the second primary outcome where it seems obvious that the authors haven’t assumed any change in the control arm, as they equal a 30 percent relative reduction from a baseline of 1.45 PIP per patient with 0.43, thus giving no room for a reduction in the control arm. This must also be clarified and commented.

**Author response**

Please see previous response.

- In my view, I find it quite unlikely that there would be no change among GPs in the control arm as they know that they are participating in this study, as they also know the objectives and outcome measures, and as they will receive a personalised list summarising PIPs. Admittedly, the authors have addressed this issue in relation to describing reasons for the additional contemporaneous national control, but I cannot see that this has influenced the sample size calculations. A clarification is needed.

**Author response**

Please see previous response.

- As mentioned above, the authors should give much clearer arguments for their claims that this is a multifaceted, complex intervention.

**Author response**

We have outlined above the reasons we feel that the intervention is a complex intervention, mainly that we feel that the process of the research pharmacist visit does meet the criteria of academic detailing, meaning the intervention comprises 4 components.

- Further, it would be of value to provide more information about how the medication review and the use of the algorithm will take place during the specially scheduled consultations. Will the GPs in any way be forced to follow the study protocol, or can they ignore this without any reminders or alerts? Are they advised to schedule a certain time for the consultation or is it up to them to decide? Has the use of the algorithm been tested and with what result? Is the patient supposed to take active part in the use of the algorithm? Is it formatted in such a way that this would be feasible?

**Author response**

We have clarified this as follows on page 8:
“The intervention consists of academic detailing, a medicines review, treatment algorithms for use during the medicines review and tailored patient information leaflets. Academic detailing can be defined as the use of a trained person from outside the practice setting who meets with healthcare professionals in their practice settings to provide information with the intent of changing their performance. [1] In this study, 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. [2] 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. 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. 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. 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. However, it does record decisions made by the GP and patient together, including the reasons for maintaining a PIP, which is a key element of this study. The components are presented in more detail in Table 1.”

The algorithm was tested in a small pilot study with 5 GPs and was found to be useful in reducing PIP. The development and piloting of the intervention will be described in a separate paper. We have clarified this as follows on page 5:

“The aim of this study is to conduct a cluster randomized controlled trial (RCT), using the Medical Research Council (MRC) guidelines for the development and evaluation of RCTs[27-28], 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, and a medicines review, utilising a web-based pharmaceutical treatment algorithm that provides recommended alternative treatment options, and tailored patient information leaflets. “The intervention was piloted with a group of five GPs and found to be feasible and acceptable within this group.”

• Finally, it would be useful if the authors could add information about how the intervention will be monitored during the phase when the GPs are performing the medication reviews. Will there be any control of how the protocol is followed or will the researchers abstain from any inference? Will participating GPs in the intervention arm be contacted if they don’t send the outcome forms as intended?
Author response
We have clarified this as follows under the Data management section 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. This study is pragmatic in nature, measuring the intervention’s effectiveness in real clinical practice.”

This study can be considered artificial in the sense that outside preparations are conducted to supply the GP (and the patient) with both essential information and a tool for decision-making to be used at a specifically scheduled visit in order to carefully consider the appropriateness of the individual patient’s medicines. It is in fact this whole process that is evaluated. The authors must therefore make clear in the Discussion whether they expect this whole process (sending lists for evaluation to an external body; feedback to prescribers; scheduling time for medication review; conducting the review with all eligible patients) to be feasible and sustainable, or whether the process has to be developed further to be applicable in routine care (e.g., by installing an algorithm directly into the medical record with prompts and warning signals).

Author response
We have clarified this as follows by adding the following to the discussion section of the paper on page 17:
There are some practical limitations to the OPTI-SCRIPT intervention. The identification of PIP in patients could be carried out by a pharmacist who could apply the criteria to patient records but this would require a formalization of the role of the pharmacist within the general practice team thus enabling access to patient records and this will have cost and service delivery implications. There are also implications for data protection when a person external to a practice, such as a pharmacist, requires access to patient records. This process could ideally, be automated, and incorporated into the various practice management systems used in primary care, along with the treatment algorithms. However, as with all computerized prompts, it would have to be designed carefully to avoid the danger of ‘alert fatigue’ which could become an issue. In addition, a medicines review process is not standard practice in Irish primary care as it is in other countries such as the UK where the National Service Framework for older people recommends that all people over the age of 75 should have their medicines reviewed at least once a year.[6] Were such a process to be introduced in Ireland, there would need to an agreement reached in terms of reimbursement mechanisms. The majority of people aged 70 and over in Ireland are entitled to free, State-funded GP care and medications (public patients). A small minority of this age group are private patients (approximately 5%), and therefore pay for their own medical care. If a medicines review process was to be introduced into standard care, an agreement would have to be reached as to whether it would be entirely State-funded or if private patients would have to incur the costs of such a service personally.
Should the OPTI-SCRIPT intervention be found to be effective, these issues would need to be taken into consideration prior to its implementation into routine care.

- The authors should follow the journal’s Instructions for Style and language, in particular not capitalize words in title or headings and sub-headings; use the same spelling (e.g., minimization – minimisation) and the same expressions (e.g., medicines review – medication review) consistently; avoid paragraphs with only one sentence in running text; and conduct proper proof-reading to avoid spelling and spacing mistakes, in particular in the figure and tables, but also in the text (e.g., form instead of from).

**Author response**
These errors have been corrected as recommended.

- Abstract – background: Clarify the age group of “older people”, as defined in the main text. Add that the prevalence of PIP relates to this age group. Clarify what “prevalence of PIP in Ireland is estimated at 36%” means. My understanding is that it means the number of individuals in the population in the defined age group that regularly “receives” at least one inappropriate medication, but this is not clearly stated.

**Author response**
We have clarified this as follows on page 2:
“Potentially inappropriate prescribing (PIP) in older people is common in primary care and can result in increased morbidity, adverse drug events, hospitalizations and mortality. In Ireland, 36% of those aged ≥ 70 years received at least one potentially inappropriate medication, with an associated expenditure of over €45 million”.

- Background: Clarify what is meant by “the prevalence of PIP in older people (aged # 70 years) in Ireland has been estimated at 36%”, as commented above. Reference #11 is not totally clear whether it refers to the whole population or those (97%?) who are listed in the database used to retrieve information about medication.

**Author response**
We have clarified this as follows on page 3:
“A recently developed explicit process measure, the Screening Tool of Older People’s Prescriptions (STOPP), has been published for use in European settings. When these criteria were applied to an Irish pharmacy claims database (containing the prescription records of 97% of those aged ≥70 nationally), 36% of those aged ≥ 70 years received at least one potentially inappropriate medication. Total PIP expenditure was estimated at over €45 million (or 9% of expenditure on pharmaceuticals in that age group).[7]”

- All abbreviations should be explained when used first time (e.g., HRB).


**Author response**
This error has been corrected.

- **Table 2**: It should be clearly indicated how prevalence was defined.

**Author response**
This has been corrected as suggested.

- **Table 3**: Should be shown on a separate page

**Author response**
This has been corrected as suggested.

- **References**: Needs to be totally revised. There are numerous errors.

**Author response**
The references have been corrected as recommended.