STUDY PROTOCOL

The effectiveness of integrating clinical pharmacists within general practice to optimise prescribing and health outcomes in primary care patients with polypharmacy: A protocol for a systematic review [version 1; peer review: 1 approved, 1 approved with reservations]

Aisling Croke¹, Oscar James¹, Barbara Clyne¹, Frank Moriarty¹, Karen Cardwell², Susan M. Smith¹

¹Department of General Practice, Royal College of Surgeons in Ireland, Dublin, Ireland
²NI Centre for Pharmacy Learning & Development, Queens University, Belfast, UK

Abstract

Introduction: Coordinating prescribing for patients with polypharmacy is a challenge for general practitioners. Pharmacists may improve management and outcomes for patients with polypharmacy. This systematic review aims to examine the clinical and cost-effectiveness of pharmacist interventions to optimise prescribing and improve health outcomes in patients with polypharmacy in primary care settings.

Methods: The review will be reported using the PRISMA guidelines. A comprehensive search of 10 databases from inception to present, with no language restrictions will be conducted. Studies will be included where they evaluate the clinical or cost-effectiveness of a clinical pharmacist in primary care on potentially inappropriate prescriptions using validated indicators and number of medicines. Secondary outcomes will include health related quality of life measures, health service utilisation, clinical outcomes and data relating to cost effectiveness. Randomised controlled trials, non-randomised controlled trials, controlled before-after, interrupted-time-series and health economic studies will be eligible for inclusion. Titles, abstracts and full texts will be screened for inclusion by two reviewers. Data will be extracted using a standard form. Risk of bias in all included studies will be assessed using the Effective Practice and Organisation of Care (EPOC) criteria. Economic studies will be assessed using the Consensus Health Economic Criteria (CHEC) list as

Open Peer Review

Invited Reviewers

1. Nagham J. Ailabouni, University of Washington, Seattle, USA
   University of South Australia, Adelaide, Australia

2. Rupert A. Payne, University of Bristol, Bristol, UK

Any reports and responses or comments on the article can be found at the end of the article.
Discussion: This systematic review will give an overview of the effectiveness of pharmacist interventions to improve prescribing and health outcomes in a vulnerable patient group. This will provide evidence to policy makers on strategies involving clinical pharmacists integrated within general practice, to address issues which arise in polypharmacy and multimorbidity.

PROSPERO Registration: CRD42019139679 (28/08/19)

Keywords
Systematic review, Polypharmacy, Multimorbidity, Pharmaceutical Services, Pharmacist, Primary Care
Introduction

Patients with multimorbidity and polypharmacy have complex health needs. Polypharmacy has commonly been defined as being on five or more medications, however recent studies have highlighted the rising prevalence of more significant polypharmacy defined as being on 10 or more medications\(^1\). Complex polypharmacy increases the risk of potentially inappropriate prescribing (PIP) and treatment burden in this patient cohort\(^2\). PIP is described as potential sub-optimal prescribing and is typically identified using screening tools such as the Screening Tool of Older People’s Prescriptions (STOPP)-Screening Tool to Alert to Right Treatment (START) criteria\(^3\), Beers criteria\(^4\) or prescribing appropriateness indices\(^5\).

Polypharmacy is also associated with adverse drug events, which may create significant cost to both the healthcare system/health service and patients\(^6\). An Irish study conducted in 2010 found that an estimated 36% of adult patients over the age of 70 had at least one PIP event. This resulted in an additional €45 million in healthcare expenditures\(^7\).

Integration of clinical pharmacists within general practices may be an effective way to address PIP, and implement deprescribing through medication reviews and address challenges with general practice workload\(^8\). Evidence suggests that clinical pharmacists improve the quality and safety of prescribing\(^9\), and that non-dispensing pharmacists integrated into the primary care setting add value to patient-centred clinical pharmacy services\(^9\). Heterogeneity of outcomes reported in systematic reviews tend to make meta-analysis challenging and thus it is unclear whether such interventions can result in clinically significant improvements in patient outcomes. There is evidence to suggest that clinical pharmacist review of medications and pharmacist-physician collaboration results in cost avoidance in the hospital setting, and that such interventions are cost-effective\(^10\). However, there is limited evidence to date surrounding the cost-effectiveness of clinical pharmacists integrated within general practice to optimise medicines and health outcomes in primary care\(^4,10\). Previous systematic reviews cite heterogeneity in terms of role, and duration and frequency of intervention as a limitation. They also focussed on interventions where the clinical pharmacist and general practitioner (GP) were geographically co-located. This systematic review will differ in that it focuses on patients with multimorbidity and polypharmacy, without a focus on specific conditions. It will include studies that involve remote clinical pharmacist and GP integration, provided there is on-going collaboration and clear evidence of working together to improve patient outcomes.

The overall aim of this systematic review is to examine the effectiveness of interventions involving the integration of clinical pharmacists within general practice, to improve prescribing practices and health outcomes in primary care settings. We will also examine the cost-effectiveness of such interventions.

Review questions

What is the effectiveness of interventions integrating clinical pharmacists within general practice on medicines optimisation and health outcomes in adult patients with polypharmacy in comparison to usual care?

Is integrating clinical pharmacists within general practice, to improve medicines optimisation and health outcomes in adult patients with polypharmacy, cost-effective?

Methods

The systematic review will be conducted in line with the PRISMA guidelines\(^11\). The protocol will be reported in line with the PRISMA-P guidelines\(^12\). Eligibility criteria

Participants/population. Patient participants must be adult patients aged 18 years and over in the primary care setting with polypharmacy as defined by study author. Patients will not be considered eligible if they are under the age of 18 or resident in a nursing home. Studies must have a majority of patients (≥80%) identified as having polypharmacy (using any definition). The generally accepted definition is five or more routine medicines\(^1\).

Clinical pharmacists participating in the intervention must be involved in medicines optimisation roles and integrated physically or remotely as per the definition below, within the primary care setting. The definition of primary care for this review will be; a system which is “integrated, easy to access, health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained and continuous relationship with patients, and practicing in the context of family and community”\(^13\). Integration will be defined as per the framework adapted from Walshe and Smith\(^14\). The framework consists of six pillars; organisational, informational, clinical, functional, financial and normative dimensions.

Intervention/exposure. To be eligible for inclusion, studies must involve a clinical pharmacist optimising medication for patients in a primary care setting through a variety of services. Interventions can be targeted at patient or prescriber behaviours. The relationship between pharmacist and GP can be conducted in a co-located setting or remotely where the pharmacist is not in the same geographical location as the GP. The relationship must be continued for the duration of the intervention. This relationship will be defined as a collaborative relationship where “health care professionals assume complementary roles and cooperatively working together, sharing responsibility for problem-solving and making decisions to formulate and carry out plans for patient care”\(^15\). Contact can be face to face, virtual, by telephone or via an online forum once the contact is in real-time.

‘Once-off’ interventions where the clinical pharmacist does not maintain a relationship with the GP will be excluded. Such interventions will demonstrate a single instance of unidirectional communication of a medication review issue to the GP (e.g. sending a fax or email) with no collaborative follow-up. We will exclude studies with interventions only targeting a single condition unless the intervention addresses all medicines for the patients, not only those medications which are condition specific.

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**Comparator/control.** Usual care in primary care setting.

**Types of studies.** We will include randomised controlled trials (RCTs), non-randomised controlled trials (nRCTs), controlled before-after (CBA), and interrupted-time-series (ITS) studies using Cochrane Effective Practice and Organisation of Care (EPOC) study design criteria[^16]. Health economic studies including comparative resource use studies and economic evaluations (cost-effectiveness analysis, cost-utility analysis, cost-minimisation analysis and cost-benefit analysis) will also be included.

**Setting.** Only studies in a primary care setting will be included. Clinical pharmacist interventions in a secondary or tertiary care setting will be excluded.

**Outcomes**

**Main outcomes.** Potentially inappropriate or high risk prescriptions (using validated indicators which may include explicit criteria such as STOPP/START[^17], Beers criteria[^18], or implicit criteria such as the Medicines Appropriateness Index[^19] and Prescribing Appropriateness Index[^20]).

**Additional outcomes.**

- Patient reported outcomes measures (PROMs): For example, Health Related Quality of Life measured using standardised questionnaires such as EQ-5D, SF-12, SF-36.
- Adverse events or harms, for example measured using the adverse drug withdrawal reaction scale[^19].
- Health service utilisation (including GP visits, emergency department (ED) visits, outpatient clinic attendances, inpatient admissions, other healthcare professional appointments).
- Clinical outcomes (physical and mental health outcomes).
- Economic evaluations;
  - Direct costs
  - Incremental cost-effectiveness ratio (ICER)
  - Cost per unit of effect
  - Quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs)
  - Cost differences (in measured in cost-benefit / cost-minimisation analysis)
  - Other economic measures where data available.

**Search strategy**

The following databases will be searched from inception to October 2019: PubMed, Cochrane Library, Cochrane Central Register of Controlled Trials, EMBASE, Web of Science, SCOPUS, Lilacs and CINAHL.

For the cost-effectiveness evaluation the following databases will be searched: NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA) database (searchable from the University of York Centre for Reviews and Dissemination site). For both PubMed and EMBASE an economic filter will be applied.

The search strategy for PubMed will include a combination of keywords and MeSH terms for broad concepts of pharmacy and primary health care. This strategy will be adapted for different databases and terms for cost-effectiveness will be included for the economic evaluation component. A review of reference lists of included studies will also be performed. No language limits will be applied. Search strategy is available as extended data[^20].

**Data management.** All citations will be downloaded and stored in EndNote reference manager, Version 8. Rayyan software will be used for the title and abstract screening step[^21].

**Study selection.** Titles will be screened for clearly ineligible studies by one researcher (AC). Titles and abstracts will be independently screened by two members of the review panel (AC and OJ) to identify studies that potentially meet inclusion criteria outlined above, following duplication removal. Studies which do not meet the inclusion criteria will be excluded at this stage. If studies are unclear or if they meet inclusion criteria, they will be selected for full text review. Where disagreement arises between reviewers, a third reviewer will be consulted (FM). A PRISMA flow chart will be used to display the flow of identified studies through the review.

**Data extraction**

Two reviewers (AC and OJ) will use a standardised, pre-piloted form (see extended data[^20]) to perform data extraction of the following information: name of first author, year of publication, country of publication, study setting; study population and participant demographics, intervention details and design, control setting details, recruitment and study completion rates, outcomes and times of measurement.

Economic evaluation data will be extracted as per the Health Information and Quality Authority (HIQA) guidelines for interpretation of economic evaluations in Ireland;
- Study question, population, intervention, comparator and setting
- Modelling methods
- Sources and quality of clinical data
- Cost data
- Resource usage
- Study outcomes
- Methods for dealing with uncertainty.

Where disagreement arises between reviewers, a third reviewer will be consulted (SS or FM).
Quality assessment
Studies will be included if they meet all inclusion criteria irrespective of quality. The risk of bias in all included effectiveness studies will be assessed using standard EPOC criteria16 (EPOC 2015) including the following domains: allocation (sequence generation and concealment); baseline characteristics; incomplete outcome data; contamination; blinding; selective outcome reporting; and other potential sources of bias. Publication bias will be assessed using a funnel plot if ten or more studies are identified.

The economic evaluation studies will be assessed for methodological quality using the CHEC list as per the Cochrane Handbook for critical appraisal of methodological quality22.

Assessing the quality of the body of evidence. The certainty of evidence for each outcome will be assessed, where appropriate, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria and GRADEPro software23.

Strategy for data synthesis
A narrative synthesis is anticipated for effectiveness studies. Similarly, for the economic evaluations a narrative synthesis is anticipated and results displayed in tables.

A statistician will advise if there are sufficient data to support meta-analysis. RevMan 5.33 or Stata version 1534 software will be used. A random effects model will be employed to account for between-study heterogeneity. As per the Cochrane Handbook35 the chi-square test will assess heterogeneity between individual studies. An I² statistic will assess the impact of heterogeneity on meta-analysis where I² value greater than 75% indicates significant heterogeneity.

Analysis of subgroups
Subgroup analysis will be performed if adequate studies exist for interventions and outcomes. Subgroup analysis will be based on age of patients (cut point of 65 years), degree of polypharmacy (<10 vs 10 or more) and location of intervention (co-located vs remote location). The effect of each individual study on the overall estimates of effect size and determinants will be assessed using sensitivity analyses.

Dissemination of information
The review will be published in a relevant peer reviewed journal, reported using the PRISMA guidelines. The review will also be presented at a relevant conference and disseminated to policy-makers, patients, and the public.

Study status
Database searches have been completed and title and abstract screening is currently underway.

Discussion
This systematic review will give an overview of the effectiveness of interventions involving clinical pharmacist integration within general practice, to improve prescribing and health outcomes in patients with polypharmacy and multimorbidity.

We will focus on interventions where the clinical pharmacist and GP work collaboratively to improve patient outcomes, whether co-located or remotely. It is intended that this will address patient populations that live in geographically isolated regions in tandem with patients who live in more geographically connected settings.

This systematic review can contribute to the evidence base for managing multimorbidity. Good quality evidence is required to develop guidelines directed at such complex patients and interventions have been focused on the patients who use clinical services most in recent years33. This review focuses on patients with polypharmacy, a factor in treatment burden for patients with multimorbidity. By addressing this issue in the primary care setting this may improve patient outcomes.

This will provide evidence to policy makers on strategies involving pharmacists integrating within general practice settings to address issues which arise in patients with polypharmacy in a primary care setting.

Data availability
Underlying data
No data are associated with this article

Extended data
Open Science Framework: The effectiveness of integrating clinical pharmacists within general practice to optimise prescribing and health outcomes in primary care patients with polypharmacy: A protocol for a systematic review. https://doi.org/10.17605/OSF.IO/38CU536

This project contains the following extended data:
- Data extraction template.xlsx (Excel file containing the data extraction sheet for the study)
- PubMed Search Strategy.docx (Word document containing the PubMed search strategy)

Reporting guidelines
PRISMA-P checklist for “The effectiveness of integrating clinical pharmacists within general practice to optimise prescribing and health outcomes in primary care patients with polypharmacy: A protocol for a systematic review” https://doi.org/10.17605/OSF.IO/38CU536

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgements
Paul J Murphy MLIS, Information Specialist, Royal College of Surgeons in Ireland Library, 26 York Street, D02 YN77. Advised on search strategies.

Grainne McCabe, Scholarly Communications & Research Support Officer, Royal College of Surgeons in Ireland Library, 26 York Street, D02 YN77. Advised on search strategies.
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Rupert A. Payne  
Bristol Medical School, Population Health Sciences, Centre for Academic Primary Care, University of Bristol, Bristol, UK

This is a generally clear, well-written protocol for a systematic review looking at the effectiveness of clinical pharmacists integrated within general practice for polypharmacy management. Overall, the methodology is sound, and the proposed review will hopefully provide a useful appraisal of the evidence.

Additional clarity could be provided around the type of clinical pharmacist in the abstract methods. The title specifically mentions integration of the pharmacist, but I think this should also be explicit in the abstract methods.

Similarly, it may be useful to expand on the definition used for integration, and to perhaps give more details regarding how the Walshe and Smith framework was operationalised, and perhaps clarifying for the reader whether all six dimensions are required without the reader having to refer to the source reference.

Further minor points:
- Clarify whether "nursing home" exclusion includes residential or other supportive care environments that don't specifically include nursing, and how situations where the setting is unclear will be dealt with.
- Outcomes - "number of medicines" should ideally be defined (although likely to vary across studies) - will it include both acute and repeat prescriptions, or account for length of treatment (e.g. chronic vs. one-off drugs)?
- The additional outcome "clinical outcomes [physical and mental health]" is very vague - some examples might help clarify what you mean by these. In particular, will they all be some sort of quantitative scale, or will be include discrete events of some description?

Is the rationale for, and objectives of, the study clearly described?
Yes

**Is the study design appropriate for the research question?**
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Partly

**Are the datasets clearly presented in a useable and accessible format?**
Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Polypharmacy, medication optimisation, clinical pharmacology and therapeutics, general practice.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Author Response 02 Mar 2020**

**Aisling Croke,** Royal College of Surgeons in Ireland, Dublin, Ireland

**Question 1**
Additional clarity could be provided around the type of clinical pharmacist in the abstract methods. The title specifically mentions integration of the pharmacist, but I think this should also be explicit in the abstract methods.

**Author response:**
The American College of Clinical Pharmacy (ACCP) defines clinical pharmacy as a ‘health science discipline in which pharmacists provide patient care that optimises medication therapy, and promotes health, and disease prevention to ensure optimal patient outcomes’ (1). Other studies have cited ‘non-dispensing pharmacists’ (2, 3) but this review cites ‘clinical pharmacist’ to capture remote interventions which may involve ‘dispensing pharmacists’. We have added text to the abstract methods on page 2 to address this comment.

**Question 2**
Similarly, it may be useful to expand on the definition used for integration, and to perhaps give more details regarding how the Walshe and Smith framework was operationalised, and perhaps clarifying for the reader whether all six dimensions are required without the reader having to refer to the source reference.

**Author response:**
Thank you for highlighting this point. We have added text to the eligibility criteria on page 5 to clarify.

**Further minor points:**
**Question 3**
Clarify whether "nursing home" exclusion includes residential or other supportive care environments that don't specifically include nursing, and how situations where the setting is unclear will be dealt with.

Author response:
A definition of nursing homes has been added to the eligibility criteria on page 4, we also outline how situations where the setting is unclear will be dealt with.

**Question 4**
Outcomes - "number of medicines" should ideally be defined (although likely to vary across studies) - will it include both acute and repeat prescriptions, or account for length of treatment (e.g. chronic vs. one-off drugs)?

Author response:
A definition has been added to the main outcomes section on page 6.

**Question 5**
The additional outcome “clinical outcomes [physical and mental health]” is very vague - some examples might help clarify what you mean by these. In particular, will they all be some sort of quantitative scale, or will be include discrete events of some description?

Author response:
We have addressed this as outlined in our response to the previous reviewer's comments and have added clarifications around these additional outcomes on page 6.

**References:**
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**Competing Interests:** No competing interests were disclosed.

Reviewer Report 03 January 2020
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Thank you for the opportunity to review this work. This is an area that requires more attention and the results of this systematic review may have positive consequences that promote increased utilisation of pharmacists in primary care settings to review and optimise medication regimens whilst reducing inappropriate medication use. I look forward to reading the findings of this systematic review.

Major Comments

Methods:
- Main outcomes: Will all of the listed different medication appropriateness criteria (explicit: STOPP/START, Beer's criteria and implicit: MAI etc.) be used to assess the medication changes of each pharmacist intervention study included in this systematic review? Can the authors please comment on what will determine the use of explicit vs implicit or the use of both explicit and implicit criteria to assess the outcomes of the included studies?

- Additional Outcomes: More clarity is needed regarding physical and mental clinical outcomes that will be used as secondary outcome measures. Please list a few specific measures as examples. What are some key clinical outcomes that would be important to consider? (e.g. Falls? Mortality? Blood Pressure? etc.)

- Since the “number of medicines” is mentioned as a major outcome of this systematic review and the introduction discusses deprescribing, is the intention to focus on the reduction of the number of medicines through pharmacist medication/deprescribing medication reviews and reduction of prescribing of high-risk medications that are inappropriately prescribed, or will potential prescription omissions as defined by the START criteria also be applied? It seems the authors intend on the later since medicines optimisation is mentioned under the heading of 'Review questions' and in the title of the study. Perhaps defining the concept of optimising medicines as reducing potentially inappropriate prescribing/sub-optimal prescribing via reducing potentially inappropriate medications (PIMs) as defined by Beer's and STOPP and potential prescription omissions (PPOs) defined by START in the introduction might provide a clearer preface for the main goal of the systematic review.

- Analysis of subgroups: Inappropriate polypharmacy and inappropriate prescribing is a common problem in older adults. Can the authors please comment on why the cut off chosen here is patients aged 65 years old? For example, is there enough evidence for cost-effectiveness of pharmacist interventions for this age population? Also, if studies that are purely older adult focused (i.e. 65 years and older) are meant to be excluded and are outside the scope of this intended systematic review, please list this explicitly under eligibility/exclusion criteria.

Minor Comments:

Abstract:
- Methods: Can the authors please clarify what is meant by 'validated indicators'? Is STOPP/START, Beer's criteria etc. what is meant? If so, please use screening tools or criteria
to assess medication appropriateness instead. Please change in the remainder of the protocol for consistency.

Introduction:
- Lines 2-3: “Polypharmacy has commonly been defined as being on five or more medications, however recent studies have highlighted the rising prevalence of more significant polypharmacy defined as being on 10 or more medications”. Whilst I agree with the content of this statement, I would recommend to:
  1. Refer to more significant polypharmacy (i.e. being prescribed or taking 10 or more medications) as hyperpolypharmacy or excessive polypharmacy as described in the literature.
  2. Please clarify that polypharmacy overall regardless of which type is on the rise in different age populations.
- Line 3: The referenced article does not mention the term ‘complex polypharmacy’, but rather the complex treatment burden associated with treating comorbidities. Please rephrase to ‘polypharmacy’ to remain consistent with the rest of the introduction.
- I would suggest combining the second paragraph beginning with “Polypharmacy is also associated with adverse drug events...” with the earlier paragraph and consolidate main concepts related to the negative consequences of polypharmacy and how polypharmacy is associated with an increased likelihood of experiencing inappropriate polypharmacy.
- Line 11: Please define deprescribing.
- Line 21: Could the authors please clarify what is meant by this systematic review will not focus on specific conditions? If previous systematic reviews focused on specific conditions (e.g. Hypertension, Diabetes etc.) could this be added to the previous sentence (line 20) that listed what other systematic reviews focused on with an appropriate reference.

Methods:
- Eligibility criteria (line 2-3): Recommend editing “Patients will not be considered eligible if they are under the age of 18 or resident in a nursing home.” to “Patients will be excluded if they are younger than 18 years old.” Will pharmacist interventions in hospital settings be excluded as well? If so, please list as an exclusion criterion. Suggestion to move text currently under the Setting heading, “Clinical pharmacist interventions in a secondary or tertiary care setting will be excluded” to this section.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.
Reviewer Expertise: Deprescribing, Pharmacist interventions, Translational Research, Geriatric Pharmacy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Mar 2020

Aisling Croke, Royal College of Surgeons in Ireland, Dublin, Ireland

Dear Editors,

Thank you very much for the constructive comments and suggestions received from the editorial team and peer reviewers. We found the suggestions very helpful and hope we have addressed any concerns raised. We have submitted a revised version of the manuscript.

We outline the specific responses to each comment as follows:

**Major Comments:**

**Question 1**

Main outcomes: Will all of the listed different medication appropriateness criteria (explicit: STOPP/START, Beer’s criteria and implicit: MAI etc.) be used to assess the medication changes of each pharmacist intervention study included in this systematic review? Can the authors please comment on what will determine the use of explicit vs implicit or the use of both explicit and implicit criteria to assess the outcomes of the included studies?

**Author response:**

Thank you for highlighting this. It is not the intention in this systematic review to apply different medication appropriateness criteria to details of medications reported in the selected studies. Studies will be included in this review where they use implicit or explicit criteria for medication appropriateness as outcomes as described by study authors. The wording in the main outcomes section on page 6 has been rephrased to clarify that these will be the main outcomes where they have been used within studies.

**Question 2**

Additional Outcomes:

More clarity is needed regarding physical and mental clinical outcomes that will be used as secondary outcome measures. Please list a few specific measures as examples. What are some key clinical outcomes that would be important to consider? (e.g. Falls? Mortality? Blood Pressure? etc.)

**Author response:**

The secondary outcome measures of interest in this systematic review have been added to the additional outcomes section on page 6 to give greater clarity.

**Question 3**
Since the “number of medicines” is mentioned as a major outcome of this systematic review and the introduction discusses deprescribing, is the intention to focus on the reduction of the number of medicines through pharmacist medication/deprescribing medication reviews and reduction of prescribing of high-risk medications that are inappropriately prescribed, or will potential prescription omissions as defined by the START criteria also be applied? It seems the authors intend on the later since medicines optimisation is mentioned under the heading of ‘Review questions’ and in the title of the study. Perhaps defining the concept of optimising medicines as reducing potentially inappropriate prescribing/sub-optimal prescribing via reducing potentially inappropriate medications (PIMs) as defined by Beer’s and STOPP and potential prescription omissions (PPOs) defined by START in the introduction might provide a clearer preface for the main goal of the systematic review.

Author response:
This systematic review will not apply explicit criteria to outcomes reported by included studies, we will report a narrative synthesis of reported outcomes or a meta-analysis where data allow. We anticipate that studies of medicines optimisation may include different outcomes for medicines optimisation. Some may use number of medicines to assess medicines optimisation, which is a crude measure that does not capture the appropriateness of any medicines stopped or started. Other studies may use reduction in PIMs or PPOs defined using explicit criteria as their measure of medicines optimisation. Within the included studies, reported data on the number of medicines at trial initiation will indicate the degree of polypharmacy in study participants. Where reported at trial end, the number of medicines will capture deprescribing or instances of a missing, clinically indicated medication being commenced. The NICE guidelines on medicines optimisation recommend the adoption of the screening tools as a part of medication review processes, alongside patient-centred shared decision making and appropriate communication with the relevant health care professionals. We have added this information to the introduction section of the paper on page 3.

Question 4
Analysis of subgroups: Inappropriate polypharmacy and inappropriate prescribing is a common problem in older adults. Can the authors please comment on why the cut off chosen here is patients aged 65 years old? For example, is there enough evidence for cost-effectiveness of pharmacist interventions for this age population? Also, if studies that are purely older adult focused (i.e. 65 years and older) are meant to be excluded and are outside the scope of this intended systematic review, please list this explicitly under eligibility/exclusion criteria.

Author response:
Thank you for clarifying this. Older age is defined by the WHO as people aged 65 years or older (1). Polypharmacy is associated with older age (2), this age group is the population most explicit criteria of prescribing appropriateness apply to, and interventions are typically performed on this age group, as such this was selected as an appropriate cut-off for subgroup analysis. This review will include all adult patients and subgroup analysis will be conducted for the patients younger than 65 years, and those who are aged 65 years and older. The wording in the subgroup analysis section on page 8 has been changed to reflect
this clarification.

**Minor Comments:**

**Question 5**

**Abstract:**

**Methods:** Can the authors please clarify what is meant by ‘validated indicators’? Is STOPP/START, Beer’s criteria etc. what is meant? If so, please use screening tools or criteria to assess medication appropriateness instead. Please change in the remainder of the protocol for consistency.

**Author response:**

Validated indicators are explicit criteria such as STOPP/START, Beers criteria, or implicit criteria such as the Medicines Appropriateness Index and Prescribing Appropriateness Index. The term validated indicators has been changed to screening tools to ensure consistency.

**Question 6**

**Introduction:** Lines 2-3: “Polypharmacy has commonly been defined as being on five or more medications, however recent studies have highlighted the rising prevalence of more significant polypharmacy defined as being on 10 or more medications”. Whilst I agree with the content of this statement, I would recommend to:

1. Refer to more significant polypharmacy (i.e. being prescribed or taking 10 or more medications) as hyperpolypharmacy or excessive polypharmacy as described in the literature.
2. Please clarify that polypharmacy overall regardless of which type is on the rise in different age populations.

**Author response:**

1. Thank you, we have replaced the term significant polypharmacy with major polypharmacy as described in the literature (3). This review does note excessive and hyper polypharmacy, however major polypharmacy is cited as the most prevalent term.
2. Text has been inserted into the introduction on page 3 to clarify the prevalence of polypharmacy.

**Question 7**

**Line 3:** The referenced article does not mention the term ‘complex polypharmacy’, but rather the complex treatment burden associated with treating comorbidities. Please rephrase to ‘polypharmacy’ to remain consistent with the rest of the introduction.

**Author response:**

Text amended to ‘polypharmacy’ as recommended.

**Question 8**

I would suggest combining the second paragraph beginning with “Polypharmacy is also associated with adverse drug events...” with the earlier paragraph and consolidate main concepts related to the negative consequences of polypharmacy and how polypharmacy is associated with an increased likelihood of experiencing
inappropriate polypharmacy.

Author response:  
As per reviewer suggestions we have combined these paragraphs and consolidated the main points on page 3.

**Question 9**  
Line 11: Please define deprescribing.

Author response:  
Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional (4). This definition has been added to the introduction section on page 3.

**Question 10**  
Line 21: Could the authors please clarify what is meant by this systematic review will not focus on specific conditions? If previous systematic reviews focused on specific conditions (e.g. Hypertension, Diabetes etc.) could this be added to the previous sentence (line 20) that listed what other systematic reviews focused on with an appropriate reference.

Author response:  
We have added text to the introduction section on page 3 to clarify this.

**Question 11**  
Methods:  
Eligibility criteria (line 2-3): Recommend editing “Patients will not be considered eligible if they are under the age of 18 or resident in a nursing home.” to “Patients will be excluded if they are younger than 18 years old.” Will pharmacist interventions in hospital settings be excluded as well? If so, please list as an exclusion criterion. Suggestion to move text currently under the Setting heading, “Clinical pharmacist interventions in a secondary or tertiary care setting will be excluded” to this section.

Author response:  
We have amended the eligibility criteria on page 4 for clarity as per reviewer comments.

**References:**  
1. Organization WH. Global Health and Ageing on-line: World Health Organization; 2011 [Available from: http://www.who.int/ageing/publications/global_health.pdf.
2. Rankin A, Cadogan CA, In Ryan C, Clyne B, Smith SM, Hughes CM. Core Outcome Set for Trials Aimed at Improving the Appropriateness of Polypharmacy in Older People in Primary Care. J Am Geriatr Soc. 2018;66(6):1206-12.
3. Masnoon N, Shakib S, Kalisch-Ellett L, Caughy GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230.
4. Reeve E, Gnjdic D, Long J, Hilmer S. A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015;80(6):1254-68.
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