PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	INTERDISCIPLINARY COLLABORATION ACROSS SECONDARY AND PRIMARY CARE TO IMPROVE MEDICATION SAFETY IN THE ELDERLY (The IMMENSE-study) – STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL
AUTHORS	Johansen, Jeanette; Havnes, Kjerstin; Halvorsen, Kjell; Haustreis, Stine; Skaue, Lillann; Kamycheva, Elena; Mathiesen, Liv; Viktil, Kirsten; Granås, Anne Gerd; Garcia, Beate

VERSION 1 – REVIEW

REVIEWER	Ulrika Gillespie Uppsala University Hospital, Sweden
REVIEW RETURNED	19-Oct-2017

GENERAL COMMENTS	It was a privilege to be asked to review this study protocol manuscript which is very clear and well written. The rational and need for the study to be performed as well as the justification for methods and design seem sound and based on the current knowledge base. I have a couple of comments and concerns however: 1. Setting The setting is not well described. What type of wards were the study wards? I did not find information on this in the manuscript. If they were acute internal medicine wards (as in the referenced study by Gillespie et al) most patients are likely to be acutely ill, at least during the start of admission, with symptoms of fatigue, dyspnoea, fever etcetera. Is it then appropriate or any point in performing the symptom assessments (to identify drug related symptoms) that is mentioned as one of the interventions? When is this done in relation to the patient journey and what are the expectations/experiences of doing this? Please explain and comment on in manuscript. Coming back to the setting; I would like to know more about the eligible patients – are they all medicine patients? And if so, is here a mixture of all diagnoses or for example cardiac or stroke or any other speciality? Has a pre-screening been performed where the number of eligible patients per week and ward was estimated along with their characteristics? This would be interesting to know. 2. Sample size The sample size is based on a study where 400 patients over the age of 80 years was included and the results from that study. However, the results from this study were only just statistically significant and the authors have stated that the sample size was, in hindsight, to small.

	Plus, patients 10 years older (80+ vs 70+) are more frequently admitted, since we consume a large proportion of hospital care towards the end of our lives, which also allows for a smaller sample size – the incidence of events is higher. In your ongoing study, you are still recruiting – my suggestion (it is perhaps not at all possible) is that you make a change in the trial registration and decide to include more patients, perhaps even twice the number, in order to be able to show results. In my opinion, it is a very worthwhile study and as such it deserves a chance to be a study that is not dismissed as being underpowered.

REVIEWER	Dr Claire Scullin Medicines Optimisation Innovation Centre (MOIC) Northern Health & Social Care Trust (NHSCT) Bretton Hall Antrim Northern Ireland
REVIEW RETURNED	01-Nov-2017

GENERAL COMMENTS	Protocol reads well and sets out a sensible approach to answering the research question. I look forward to reading the final published manuscript. Would like to see the standardized tools that are being utilized for MedRed, symptom evaluation and DRP Identification. Additional word line 46, page 9 (Experience).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Setting
1. What type of wards were the study wards?
We are including patients from two acute internal medicine wards. The ward at UNN Tromsø is a geriatric internal medicine ward, caring for older individuals with complex acute medical needs. The ward at UNN Harstad is a general internal medicine ward caring for patient suffering from different diseases such as stroke, pulmonary-, kidney- and endocrine diseases as well as geriatric concerns.

Response: We have added this information in the revised manuscript.
Old version (page 4; 47-49):
The study is carried out at two different locations at the University hospital of North-Norway (UNN); UNN Tromsø and UNN Harstad.
New version.
The study is carried out at two acute internal medicine wards at the University Hospital of North-Norway (UNN); a geriatric internal medicine ward at UNN Tromsø and a general acute internal medicine ward at UNN Harstad. The geriatric ward cares for older patients with complex acute medical needs and has consultants specialized in geriatric medicine. The general medicine ward treats patients admitted for stroke, pulmonary-, kidney- and endocrine diseases as well as patients with geriatric concerns.

2. If they were acute internal medicine wards most patients are likely to be acutely ill (….). Is it then appropriate or any point in performing the symptom assessments (to identify drug related symptoms) that is mentioned as one of the intervention?

Response: The inclusion of a symptom assessment is based on The Lund integrated medicines management model described in reference 21. The function of the symptom assessment is to reveal symptoms related to adverse reactions of medications, and forms part of the basis for the medication review. We also ask about symptoms before admission, and consequently it does not only refer to the present state. We have added this information in the revised manuscript.
Old version (page 6;42-43):
The evaluation seeks to answer whether and to what degree patients are experiencing any of the following ten symptoms that may be related to medication therapy
New version:
The symptom assessment is performed to reveal if a patient recently has experienced any of the following ten symptoms potentially related to medication therapy.

3. When is this (symptom assessment) done in relation to the patient journey and what are the expectations/experiences of doing this?

Response: The symptom assessment is normally done in relation with the medication reconciliation interview, as early as possible after inclusion, but depending on the state of the patient this may vary. One of the effect measures in our study is health related quality of life, and we suspect that if the patients are experiencing symptoms asked for in the symptom assessment, this may affect this parameter negatively. Also, if they experience any symptoms at home, we can easier address these concerns during the medication review. We have added a sentence regarding this in the revised manuscript.
Old version (page 6;40-41):
During MedRec, the study pharmacists also perform a standardized symptom evaluation to be used in Step 2.
New version:
During MedRec, the study pharmacists also perform a standardized symptom assessment to be used in Step 2. This is done to identify possible adverse drug reactions, or possible targets for medication therapy improvements from a patient perspective

4. I would like to know more about the eligible patients – are they all medicine patients?

Response: Yes, they are all medicine patients. This has been addressed in comment nr 1, where we explain that the included patients are from the " The geriatric internal medicine ward at UNN Tromsø and the general acute medical ward at UNN Harstad".

5. And if so (all medical patients), is here a mixture of all diagnoses or for example cardiac or stroke or any other speciality?

Response: Yes, there is a mixture of all diagnoses, see comment nr 1. We have chosen not to focus on any disease-specific patient group in particular, except for patients 70+ years.

6. Has a pre-screening been performed where the number of eligible patients per week and ward was estimated along with their characteristics?

Response: We know from 2015-numbers that the geriatric ward at UNN Tromsø has approximately 550 individual admissions annually, and that the medicine ward at UNN Harstad has approximately 1700 individual admissions annually.

Some of these patients will be below 70 years and not eligible for inclusion. However, as the inclusion criteria are wide we have estimated that we should have enough patients to include 500 patients over a two year period.

Sample size
We welcome the discussion from the reviewer regarding the sample size calculations and concerns about an underpowered study.
Since we lack data on the rate of hospital visits in our population, we have estimated that our population has the same event rate as in the referenced study (ref 12). The reviewer argue that this may potentially lead to an overestimation of the event rate in our population as the age of patients may be lower in our study because of lower inclusion age (≥80 in referenced study and ≥70 in our study). The majority of included patients in our study will likely be from the Geriatric internal medicine ward were patients by experience on average are over 80 years, and quite fragile. We are therefore not certain that the average age (and event rate) will be much lover in our study than in the study by Gillespie at al. even though we have a lower inclusion age.
The study by Gillespie at al, with a similar type of intervention as ours, was able to show a 16% reduction in the rehospitalization rate. We have assumed that our intervention could show a similar effect, and powered our study for this. The reference study had a sample size of 400 patients, and we will include 500 patients, an increase in sample size of 20 %. To double the number of patients included, as suggested, will only give a modest increase in the study power but, we are sad to say, increase study costs well above our funding.

Reviewer 2
Would like to see the standardized tools that are being utilized for MedRec, symptom evaluation and DRP-identification.
The standardized tools are developed in Lund, Sweden and translated into Norwegian. Because they are not published by the developers, we do not feel that we can translate them to English and publish them ourselves. However, we are in contact with the developer to see if we could do this together at a later time. We have described the tools in the manuscript (p.6-7), and are happy to give more information if necessary. For further access to the tools by readers, we have referred to the research group in Lund, Sweden and Professor Tommy Eriksson who is one of the main founders. We have uploaded our Norwegian documents to ScholarOne for the editors to see, and hope that editors can forward them to the reviewer. We kindly request that these documents are not published.

Changes made by us
In addition to the reviewer comments, we have revised language, spelling and grammar, and implemented a more consistent terminologi using medications instead of drugs, and admissions/hospital stay/readmissions instead of hospitalization/re-hospitalization. We have moved one author (KHH) from place 9 to 3 in the authors order, in agreement with all the coauthors.

VERSION 2 – REVIEW

REVIEWER	Ulrika Gillespie Uppsala University Hospital, Uppsala, Sweden
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	I find the modifications and clarifications that you have added in the revised version satisfactory.