PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Integrating the clinical pharmacist into the emergency department interdisciplinary team: A study protocol for a multicentre trial applying a non-randomized stepped wedge study design.
AUTHORS	Vesela, Renata; Elenjord, Renate; Lehnbom, EC; Ofstad, Eirik; Johnsgård, Tine; Zahl-Holmstad, Birgitte; Risør, Torstein; Wisløff, Torbjørn; Røslie, Lars; Filseth, Ole Magnus; Valle, Per-Christian; Svendsen, Kristian; Frøyshov, Hanne Mathilde; Garcia, Beate

VERSION 1 – REVIEW

REVIEWER	De Winter, Sabrina KU Leuven University Hospitals Leuven
REVIEW RETURNED	11-Mar-2021

GENERAL COMMENTS	This is a very interesting and a valuable protocol. The authors have done a very good job and I wish them a lot of succes with their study. I am looking forward to see the results. Some small remarks that need some clarification. 1. If the order of the inclusion of the ED was changed, would it have an impact on the results? 2. Their might be some confounding factors. Is the "rush" and are the waiting times of the three emergency departments the same? Are their any seasonal factors to take into account? 3. How do you guarantee that every clinical ED pharmacist performs similar interventions? Which guidelines or tools are used? Please add some references if it is the case. How do you ensure that the clinical ED pharmacist is up-to-date with the latest guidelines? 4. Will every pharmacist intervention consist of medication reconciliation, medication review, drug therapy recommendations, guide drug administration, teaching/counselling? Might it introduce a bias if there is some inconcistency? 5. Do you have an idea of the pharmacist's capacity? Will it be enough to cover every patient admitted to the ED? What do you do with patients who were discharged from the ED before an assignment to a pharmacist has taken place? Might it introduce a bias?

REVIEWER	Acquisto, Nicole University of Rochester Medical Center
REVIEW RETURNED	21-Mar-2021

GENERAL COMMENTS	2.2 - will the EM pharmacist be with the EM physician and nurse in the initial evaluation of the patient?

	2.3 - how is it anticipated that the impact of the pharmacist will be evident if the patient is not receiving direct services? 2.6 - is the pharmacist able to reconcile medications independent of the clinicians? Are the pharmacists only targeted in ED patients that will likely be admitted or any ED patient? It may be most valuable to only target those likely to be admitted to the hospital. 3.2 - is there currently a delay in admission to the hospital due to medication review/reconcilliation being performed? Does this need to occur before admission? How is it anticipated that these activities performed by the pharmacist in the ED will effect total length of stay, especially when there may be clinical pharmacists that are involved once the patient is admitted to the hospital. Would consider what aspect of care the ED pharmacist is solely likely to effect. Time to rehospitalization - It seems that the pharmacist could effect if this occurs or not, but how is it anticipated that the time to rehospitalization would be effected? It seems that the pharmacist may have the most impact on the total time in the ED and ED representations, but less on hospital LOS. Would reconsider the composite endpoint and have the more ED focused endpoints as the primary and a composite including hospital LOS as a secondary.

REVIEWER	El Hajj, Maguy Qatar university College of Pharmacy, Clinical Pharmacy and Practice
REVIEW RETURNED	07-Apr-2021

GENERAL COMMENTS	Thank you for your invitation. Please find my comments below - Please ensure that the manuscript sections and references are in line with the journal requirements Introduction - The first paragraph has to be well referenced - There are many studies that demonstrate the effectiveness of ER pharmacist. These should be added and cited. - Please add more information about the status of clinical pharmacy and pharmacy practice in Norway. Hypothesis - The study outcomes should be measurable. How can we assess that the intervention will increase the appropriateness of medication therapy and improve transfer of medication-related information to the next level of care? How can we measure this? - What kind of intervention are we talking about? Methods - Please add more information on why this specific design was added: non-randomized stepped wedge trial design - More information on hospital practice should be provided in the methods section - Please add more information about the intervention. What are the components of the intervention? Any theoretical frameworks that shape the intervention? What is the pharmacist is supposed to do? - How outcomes will be assessed/ through phone calls or medical records? - Whoever is assessing outcomes is going to be blinded for the study groups? - More information should be added to study analysis: how to account for potential differences or confounding between the two groups? Discussion

	- The discussion should be restricted with no bullet points - Please add the implications of this study on hospital and clinical practice in Norway - There are several studies that were published on this topic how this study is different - Please include the limitations of this study References - Many of the references are old. Please replace them with newer ones.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Sabrina De Winter, KU Leuven University Hospitals Leuven Comments to the Author:
This is a very interesting and a valuable protocol. The authors have done a very good job and I wish them a lot of succes with their study. I am looking forward to see the results.

Some small remarks that need some clarification.

1. If the order of the inclusion of the ED was changed, would it have an impact on the results?

Reply from authors: This is a good question. The order should not have an impact on the results as long as the effect is similar in the three EDs. We have no reasons to believe that it would differ and no prior knowledge to predict where any differences would occur in that case.
However, changing the order would indeed decrease the statistical power, meaning the ability to detect the effect we want to study. Possibly, the working environment in the ED and how successfully pharmacists are integrated in the ED team will have a greater impact. We decided on this order of inclusion, from the largest ED to the smallest, to cover more patients and consequently collect more data. The order of the EDs have been optimized with this in mind as well as with the purely practical matter of knowing in advance when to hire and train pharmacists for the different study sites. Theoretically, it would have been advantageous to have random order of inclusion of EDs but this is impossible with the requirement of each site to hire and train pharmacists and prepare the EDs to have workstations for the pharmacists ready.

2. Their might be some confounding factors. Is the "rush" and are the waiting times of the three emergency departments the same? Are their any seasonal factors to take into account?

Reply from authors: This is an interesting point you raise. There is a difference in size of the three departments and in the number of admitted patients. However, we do not believe that the number of patients admitted will change very much during the study period and as such will not be an issue. While there should be few if any systematic differences between persons having to go to the ED during the study period, there will be some changes in who is admitted related to the season. Changes such as a slight increase in proportion of patients with fractures during winter. Calendar month will be included as a categorical covariate in the analyses to adjust for these types of effects. This has been made clearer in Statistics and Data analysis sections.

3. How do you guarantee that every clinical ED pharmacist performs similar interventions? Which guidelines or tools are used? Please add some references if it is the case. How do you ensure that the clinical ED pharmacist is up-to-date with the latest guidelines?

Reply from authors: Thank you for your important question. We have now tried to explain this, and your next question, better in the manuscript. The pharmacists involved in the study are experienced clinical pharmacists, with work experience from various hospital departments. They are going to

perform similar clinical tasks as they did on the wards before, e.g., applying the standardized IMM methodology to perform medicines reconciliation, medication review, and patient counselling. To make sure the pharmacists are up-to-date and have a similar approach regarding the intervention, they have received special training prior to the intervention, focusing on ED related specialities. Keeping up-to-date knowledge and being familiar with the latest guidelines is a standard requirement for all pharmacists in Norway and is assured by regular courses, meetings and scientific seminars.

4. Will every pharmacist intervention consist of medication reconciliation, medication review, drug therapy recommendations, guide drug administration, teaching/counselling? Might it introduce a bias if there is some inconcistency?

Reply from authors: Thank you for this important comment, we have reworded section 2.6. Standardized procedures to make this easier to understand. This is a complex intervention with a pragmatic approach where the intervention itself is not standardized, which better reflects the real-world setting. Inclusion of pharmacists in the team can lead to additional changes in the service when physicians and nurses use the pharmacists as a resource. Each patient will require different clinical interventions. Therefore, how, when and which task will be performed for each patient cannot be predetermined, but must be decided by the pharmacists based on patient's needs and time constraints. Thus, not every patient will receive the same intervention by the ED pharmacists, and not every nurse or physician would get discuss the same medication related issues with the ED pharmacists. The ED as a unit will be providing an extended service during the intervention period. A bias of inconsistency is of course relevant, but we believe that an intervention close to real-world is the most appropriate way of studying a complex intervention.
5. Do you have an idea of the pharmacist's capacity? Will it be enough to cover every patient admitted to the ED? What do you do with patients who were discharged from the ED before an assignment to a pharmacist has taken place? Might it introduce a bias?

Reply from authors: We do not have an idea of the pharmacists' capacity but expect them to be unable to cover all patients at all time. We do anticipate that their capacity will increase over time as they get more familiar with the ED and the team working there. Data on how many patients pharmacists were able to cover will be collected at the end of this study. We have, however, made sure that there will be two pharmacists available in the EDs during mid-day when the majority of the patients are admitted.

Reviewer: 2
Dr. Nicole Acquisto, University of Rochester Medical Center Comments to the Author:

2.2 - will the EM pharmacist be with the EM physician and nurse in the initial evaluation of the patient?

Reply from authors: Thank you for this question. Because of national electronic systems and databases, the ED pharmacists are able to partly review patient's medications before the patient reaches the ED. Based on results from this evaluation, and if needed, the ED pharmacist can be present for the initial evaluation together with the ED physician and nurse. Nevertheless, this is not a general requirement. However, our experience is that valuable information about medication use emerges when the pharmacists talk to patients, and we do focus on the medication reconciliation process performed by the pharmacist. This should be done as soon as possible, but not necessarily simultaneously with other evaluations.

2.3 - how is it anticipated that the impact of the pharmacist will be evident if the patient is not receiving direct services?

Reply from authors: This is a very valuable comment, we have tried to better express our intention and revised section 2.6 of our manuscript. To not introduce any misunderstandings; many (and hopefully a large proportion) ED patients will be receiving direct service from the pharmacists. However, some may not due to time constraint, unnecessity or other factors. Some may also only be discussed in the ED team involving the pharmacist. As this is a complex intervention with a pragmatic and real-world approach, we believe that the inclusion of a pharmacist in the team can lead to additional changes in the service. The team members will also learn from the pharmacists, and apply their knowledge on the next patient, even if the pharmacists have not been directly involved. Each patient will require different clinical interventions. Therefore, how, when and which task will be performed for each patient cannot be predetermined, but must be decided by the pharmacists based on patient's needs and time constraints. Thus, not every patient will receive the same intervention by the ED pharmacists, and not every nurse or physician would get discuss the same medication related issues with the ED pharmacists. The ED as a unit will be providing an extended service during the intervention period. So, it is not that we expect to see an impact of the clinical pharmacists, but we are hoping to see an effect of the extended service, of which the ED pharmacist is being part of.
2.6 - is the pharmacist able to reconcile medications independent of the clinicians? Are the pharmacists only targeted in ED patients that will likely be admitted or any ED patient? It may be most valuable to only target those likely to be admitted to the hospital.

Reply from authors: This is a very good point. The pharmacists are partly able to reconcile medications independent of the clinicians, but the results and potential amendments of the medication list need to be discussed with the physician. The physician will also need to make the final changes to the medication list. In addition, medication review starts at the same time and other elements of the therapy may need to be discussed as well. Consequently, this is a team work where the pharmacist plays an important role as a support for the physician.
You are right that the ED pharmacists should focus on the patients who are about to be hospitalized. However, in reality it is very difficult to determine, which patient will be hospitalized and which will be released, the first hour or so after their admission to the ED. And it is during patients' first hour, the ED pharmacists usually get to talk to them. However, two of three patients admitted to the EDs are also admitted to the hospital. On the other hand, many of the patients who are not admitted to hospital will sometimes revisit the ED, making work done for these patients by the pharmacist not wasted.

3.2 - is there currently a delay in admission to the hospital due to medication review/reconcilliation being performed?

Reply from authors: Thank you for your questions. We have chosen to answer them separately.

We do not know this, as this will be part of our study results. However, we do believe there will not be any more delays due to the ED pharmacist, as the pharmacist can work while the patients are awaiting the physician or other evaluations. In the contrary, we are hoping that the pharmacists will be able to speed up the process of patient admission.

- Does this need to occur before admission?

Reply from authors: MedRec should be performed as soon as possible during hospitalization, wrong medication use may actually be the reason for the admission. If it is done in the ED, any issues with medication use is identified immediately. Also, not all hospital departments have a pharmacist, and consequently MedRec by pharmacists will not be performed. If the pharmacists do not have time to

perform the MedRec, or have additional questions that have not been solved, they are able to write this in the patient journal so that the hospital department can continue the pharmacists' work.

- How is it anticipated that these activities performed by the pharmacist in the ED will effect total length of stay, especially when there may be clinical pharmacists that are involved once the patient is admitted to the hospital. Would consider what aspect of care the ED pharmacist is solely likely to effect.

Reply from authors: This will also be part of the study results, and we might actually see that total length is increased. This is also valuable information. However, we do not believe in an increase. If medication related problems are identified by the pharmacist work in the ED, these can be solved immediately and length of stay may be reduced. Many published studies support this hypothesis, e.g, the study by Hohl et al., which we have used for our power calculations.

- Time to rehospitalization - It seems that the pharmacist could effect if this occurs or not, but how is it anticipated that the time to rehospitalization would be effected?

Reply from authors: This will also be part of the study result, as above, and we do not know before the study has been performed. It is important to make medication use correct, and we believe that the ED pharmacist may have an impact. The ED visit is important for how the patient is treated during hospitalization. A better medication use and management may reduce time to hospitalization.

- It seems that the pharmacist may have the most impact on the total time in the ED and ED representations, but less on hospital LOS. Would reconsider the composite endpoint and have the more ED focused endpoints as the primary and a composite including hospital LOS as a secondary.

Reply from authors: We are grateful for the reviewer comments about our endpoints, and share some of the arguments for discussion. However, we do not necessarily agree with the endpoints suggested. Our primary endpoint agrees with the published Canadian study where pharmacist led medication review reduced time in hospital among high-risk patients under 80 years of age (Impact of early in-hospital medication review by clinical pharmacists on health services utilization, Hohl et al.). Time in hospital includes both LOS and time to rehospitalization. Consequently, it is important for us to study both elements in our composite endpoint as secondary endpoints. We have made some revisions in our manuscript, section 3.2, mainly to clarify for the reader.

Reviewer: 3
Dr. Maguy El Hajj, Qatar university College of Pharmacy Comments to the Author:
Thank you for your invitation. Please find my comments below

- Please ensure that the manuscript sections and references are in line with the journal requirements

Reply from authors: Yes, thank you. This has been done.

Introduction
- The first paragraph has to be well referenced

Reply from authors: Thank you. There have been added more references.

- There are many studies that demonstrate the effectiveness of ER pharmacist. These should be added and cited.

Reply from authors: Thank you. The manuscript has been revised accordingly.

- Please add more information about the status of clinical pharmacy and pharmacy practice in Norway.

Reply from authors: We have added a sentence about the status of clinical pharmacy in EDs in Norway, please see the answer to the comment below about More information about hospital practice should be provided.

Hypothesis

- The study outcomes should be measurable. How can we assess that the intervention will increase the appropriateness of medication therapy and improve transfer of medication-related information to the next level of care? How can we measure this?

Reply from authors: Thank you for your valuable comment. The hypothesis section has been revised. Our hypothesis is that the intervention will affect time in hospital during 30 days after admission to the ED, combining time in ED during stay, time in hospital during stay if hospitalized and time in ED and/or hospital if rehospitalized within 30 days after each ED admission. This in turn will reduce time before the first unplanned rehospitalization, number of hospital re-admissions, and mortality, which again may reduce health care costs.

- What kind of intervention are we talking about?

Reply from authors: Thank you for your question, we understand that this may be confusing. However, the intervention is to introduce the pharmacist in the ED. We have not completely decided the exact content of the pharmacist work, as it is a pragmatic and real-world approach that cannot be completely decided as it depends upon the team and the patients. Each patient will require different pharmacist services. How, when and which task will be performed for each patient cannot be predetermined, but must be decided upon and adapted to patient's needs and time constraints. Thus, not every patient would receive the same intervention by the ED pharmacist, and not every nurse or physician would get discuss the same medication related issues with the ED pharmacist, however, the ED as a unit will be providing an extended service during the intervention period. The intervention may involve (as stated in section 2.6) standardized procedures, like the integrated medicines management (IMM) methodology. IMM involves medicine reconciliation, medication review, patient counselling and collaboration with the interdisciplinary team. We have now revised the manuscript section 2.6 and hope this is easier to understand.

Methods

- Please add more information on why this specific design was added: non-randomized stepped wedge trial design

Reply from authors: Thank you for your comment here, we hope we have managed to explain better now in the revised section 2.1. The stepped-wedge trial design was chosen due to the limitations of randomized controlled designs as described in literature, e.g., by Cook and Thigpen https://www.tandfonline.com/doi/full/10.1080/10669817.2019.1589697. The investigation of complex interventions in health care will require other designs, where the stepped-wedge design is suggested as one of the most appropriate as it allows for both horizontal and vertical adjustments. This has been described in the manuscript, section 2.1 (A stepped wedge design allows for the intervention to be rolled out sequentially, thus allowing to control for differences between study sites (vertical control)

and long-lasting impacts (horizontal control) during the study period. This is the gold standard when a conventional randomized controlled trial is not possible). The implementation of a clinical pharmacist into the ED interdisciplinary team is a complex intervention where interactions between the pharmacist and the rest of the team will change how the overall service is provided in addition to the tasks that the pharmacist will introduce into the ED. The number and variability of outcomes also point at the complexity of the intervention. Therefore, there has been permitted a degree of flexibility and tailoring. The effect of the intervention will be assessed applying a non-randomized stepped wedge trial design.

- More information on hospital practice should be provided in the methods section

Reply from authors: See section 2.2. for information about hospital practice in Norway. We have now included a sentence about pharmacist availability in EDs and hospital wards, and hope this would be appropriate to answer your question.
"Norway has a well-functioning primary care system, including municipal urgent care clinics providing ambulatory care outside of general practitioner (GP) office hours. In order to be admitted to the ED, the patients need a referral either from GP or from a physician at an urgent care clinic. At the ED, the patient is met by an ED nurse and an ED physician (either an intern or a resident in specialty training), who perform the initial examinations and assessments of the patient. A senior physician is always on call in case of the need for a consultation. NLSH is the only ED with senior physicians situated in the ED during day-time. From the ED, patients are either admitted to a hospital ward, transferred to a municipally run health institution or discharged to their homes". Few EDs in Norway have pharmacist included in the interdisciplinary team, and many hospital wards do not have clinical pharmacist available.

- Please add more information about the intervention. What are the components of the intervention? Any theoretical frameworks that shape the intervention? What is the pharmacist is supposed to do?

Reply from authors: Thank you for your additional questions, the manuscript has been revised in the section 2.6 to better explain the intervention. There is no theoretical framework, only a methodological framework; the IMM methodology. The ED pharmacists will collaborate with the interdisciplinary teams and perform the following tasks according to patients' and EDs' needs: medication history taking, medication reconciliation, medication review, drug therapy recommendations, guidance on drug administration, medication information and counselling to patients/next of kin and health care personnel and communication about medications and changes in medication regimes. Standardized procedures, like the integrated medicines management (IMM) methodology, will be applied where possible. However, this is a complex intervention, where the inclusion of a pharmacist in the team can lead to additional changes in the service when physicians and nurses use the pharmacist as a resource. Each patient will require different tasks as assessed by the pharmacist. Therefore, how, when and which task will be performed for each patient cannot be predetermined, but must be decided upon and adapted to patient's needs and time constraints. Thus, not every patient would receive the same intervention by the ED pharmacist, and not every nurse or physician would get discuss the same medication related issues with the ED pharmacist, however, the ED as a unit will be providing an extended service during the intervention period.

- How outcomes will be assessed/ through phone calls or medical records?

Reply from authors: This has already been answered in the manuscript section 3.4 (an overview in Table 1), but we completely understand the question. In Norway, we have very good data systems and national registries. The outcome data will consequently be collected retrospectively from patient records and these registries. This form of data collection has been approved by the ethical committee.

- Whoever is assessing outcomes is going to be blinded for the study groups?

Reply from authors: During assessing outcomes, the statistician will be blinded for study group allocation. We have amended section 3.5 of the manuscript.

- More information should be added to study analysis: how to account for potential differences or confounding between the two groups?

Reply from authors: We do not expect there to be any systematic differences between whoever comes to the emergency department before starting the intervention and while the intervention is running, and as the number of patients are large random differences should also be minimal. However, any time related trends will be handled by including calendar months in the analysis. This has been made clear in the statistical analysis part of the methodology with changing the sentence: "Regression modelling will be used to adjust for potential confounders such as calendar time, this will be done using generalized estimating equations (GEE) in order to accommodate the cluster nature of the data."

Discussion

- The discussion should be restricted with no bullet points

Reply from authors: This has been revised.

- Please add the implications of this study on hospital and clinical practice in Norway

Reply from authors: Thank you, we agree. We have revised the discussion section, and added the following, also based on the next two questions:
This is the first study located in literature testing a pragmatic real-world pharmacist approach, including all patients going through the ED throughout a whole year. Results will give valuable insight into outcomes of ED pharmacist involvement, and positive results may add speed to the implementation of pharmacists in ED settings world-wide. The main strength of the study is the stepped-wedge design, allowing for inclusion of the total population going through the ED in the study period. Another strength is the unbiased endpoint data collection from high quality national registers. Some limitations do however exist, the main one being the inclusion of the pharmacists in the ED team. If they are not properly included, they may not be able to fully perform pharmacist services and consequently not able to influence patient care. Regarding generalizability, we believe results may have implications for both Norway, Scandinavia and other countries with a similar ED and hospital structure.

- There are several studies that were published on this topic how this study is different

Reply from authors: We agree with the reviewer comment, there are several studies investigating ED pharmacist involvement. However, this is the first study with a pragmatic real-world approach including all patients going through the ED throughout a whole year, i.e. 30.000. See revision suggested above based on the previous comments.

- Please include the limitations of this study

Reply from authors: Thank you, this has now been included. See revised section 5.

- Many of the references are old. Please replace them with newer ones.

Reply from authors: Thank you, references have been replaced.

VERSION 2 – REVIEW

REVIEWER	De Winter, Sabrina KU Leuven University Hospitals Leuven
REVIEW RETURNED	23-Aug-2021

GENERAL COMMENTS	The questions have been answered correctly.