The Emergency Department (ED) pharmacist for improvement of under- and overtreatment with medication

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PROTOCOL TITLE 'The Emergency Department (ED) pharmacist for improvement of under- and overtreatment with medication'

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Independent expert (s)	***n.a.***
Laboratory sites <*if applicable*>	***n.a.***
Pharmacy <*if applicable*>	***n.a.***

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
ED	**Emergency Department**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
N.a.	**Not applicable**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Medication related harm can lead to a substantial number of hospital admissions in The Netherlands. An important risk factor is polypharmacy, and associated under- and overtreatment with medication. Medication reviews can help improve under- and overtreatment, but are not very costeffective when used in primary prevention of medication related hospital admissions. Medication reviews by an emergency department (ED) pharmacist in patients visiting the ED due to a medication related problem (i.e. secondary prevention) is likely to be costeffective, but studies proving this assumption are lacking.
Objective: To study the effect of medication reviews by an ED pharmacist on under- and overtreatment in patients admitted to the ED because of a medication related problem. Secondary objectives are to study the effect of an ED pharmacist on: readmissions, costs, quality of life and recognition of medication related problems in the ED.
Study design: Intervention study, with a within patient pre-post design.
Study population: Patients (≥18 years) visiting the ED of two Dutch hospitals (Erasmus MC Rotterdam and OLVG-West Amsterdam) because of a medication related problem.
Intervention (if applicable): Implementation of an ED-pharmacist who will be responsible for recognition of medication related problems and for medication review in order to optimize medication use by the patient.
Main study parameters/endpoints: Percentage of patients in which under- and overtreatment could be reduced. Secondary outcomes: medication related readmissions, cost, quality of life and percentage of medication related admissions that are recognized as such.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: As this is a quality of care project not influencing patient's integrity, no burden and risks are associated with participation. Patients benefit by having their medication reviewed.

1. INTRODUCTION AND RATIONALE

The Dutch Multicenter HARM-study showed that every year 36,000 patients are being hospitalised due to medication related problems, of which about 16,000 are potentially avoidable [1]. During the HARM-study a specially developed triggerlist was used to identify medication related hospitalisations. In a subsequent study the HARM triggerlist was expanded, resulting in increased detection rates [2]. However, in everyday routine doctors do not use such triggerlists and thus the patient's symptoms are not always recognised as being induced by their medication. In literature, the frequency of medication related hospitalisations is on average 5.35% in studies using the same methodology as the HARM-study [3]. In contrast, studies relying on recorded doctors' diagnoses show frequencies of 0.14-1.83% [3]. This suggests that a substantial degree of underdiagnosis exists. Several studies looking specifically into this topic of recognition of adverse drug events (ADEs) confirm that ADEs are not well recognised by doctors. In a French teaching hospital, Roulet et al found that only 35% of ADEs were identified by emergency department (ED) physicians. This was especially the case when the drug was involved in a multifactorial pathological condition [4]. In a Swiss population this percentage of recognition of ADEs by emergency physicians was 40% [5], while in a Canadian study this percentage was somewhat higher with 62% [6]. In another Canadian study by Hohl et al. a slightly lower percentage of 51% was found [7]. In conclusion, 38-65% of ADEs are not recognized in emergency departments. Non-recognition will compromise patient outcome. First of all, the causative agent is not stopped. Furthermore, the symptoms may lead to unnecessary diagnostic procedures and to symptomatic treatment with unnecessary medication. All of these factors form a threat to patient safety and may lead to increased duration of hospital stay. Introduction of a pharmacist on the emergency department, who can identify ADEs using a combination of the HARM study trigger list and his clinical pharmacological skills may enhance the recognition of ADEs and improve patient safety. Besides increasing the recognition of ADEs, an ED pharmacist could also take care of medication review, thus not only stopping the causative agent, but also improving additional under- and overtreatment that could cause problems in the future. In addition, the ED pharmacist can take care of communication of the ADE, the causative agent and the problems solved in the medication review to other healthcare providers both in- and outside the hospital. This may assist in tackling another important problem regarding ADEs: even when they are recognised, a risk of represcription of the causative agent exists due to insufficient communication to other healthcare providers. Van der Linden et al showed that 27% of medicines stopped because of an ADE were represcribed; for serious ADEs this percentage was 22% [15]. Finally, the ED pharmacist will involve the patient in assessing and preventing the ADEs and counsel on the reasons for adding medication (improving undertreatment) and stopping medication (improving overtreatment) using the teach-back method [16] to confirm that the patient has understood how the ADE can be prevented and why medication has been changed.

2. OBJECTIVES

Primary objective of the study is to reduce under- and overtreatment (including stopping/switching of causative agent for the medication related ED visit) by implementing an ED pharmacist.

Secondary objectives are:

- To study the effect of the ED pharmacist on medication related readmissions
- To study the effect of the ED pharmacist on costs
- To study the effect of the ED pharmacist on quality of life of the patients
- To study the effect of the ED pharmacist on the degree of recognition of a medication related cause of the ED visit.
- To study the patient's perspective on his or her experience with the intervention.

STUDY DESIGN

Intervention study, with a within patient pre-post design.

All included patients will receive the medication review intervention by the ED-pharmacist.

Medication use and hospitalisations (and other outcomes) in 6 months before the intervention will be compared with the same outcomes in 6 months after the intervention after the intervention.

3. STUDY POPULATION

3.1 Population (base)

All patients visiting the ED's of the Erasmus MC Rotterdam and OLVG-West Amsterdam.

3.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Visiting the ED due to a medication related problem. Medication related causes of the ED visit will be detected by using an updated version of the HARM trigger list.

3.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients not using medication
- Patients younger than 18 years.
- Patients not admitted to hospital following the ED-department visit
- Patients already included in the before-intervention period will be excluded for the after period.; patients in the after-period can only be included once.
- Patients with intentional drug poisoning.

3.4 Sample size calculation

Studies looking into the effect of medication review tools have included a minimum of 100 patients [16]. With a detection rate of 5% medication related ED visits, in total 2000 ED visits need screening (1000 per hospital). Given the number of ED visits in each hospital, this is feasible within 6 months (ED-pharmacist will only work during work-days; i.e. 130 working days within 6 months; thus 8 visits to be screened per day).
Ten patients will be interviewed to study the patient's perspective on the intervention.

4. TREATMENT OF SUBJECTS

4.1 Investigational product/treatment

The implementation of an ED-pharmacist who will be responsible for:

- Recognition of medication related ED visits
- Performing a medication review (involving the patient), aimed at stopping/switching the causative agent and aimed at reducing under- and overtreatment
- Communication to next healthcare provider
- Communication to patient.

4.2 Use of co-intervention (if applicable)

N.a.

4.3 Escape medication (if applicable)

N.a.

5. INVESTIGATIONAL PRODUCT

N.a.

5.1 Name and description of investigational product(s)

N.a.

5.2 Summary of findings from non-clinical studies

N.a.

5.3 Summary of findings from clinical studies

N.a.

5.4 Summary of known and potential risks and benefits

N.a.

5.5 Description and justification of route of administration and dosage

N.a.

5.6 Dosages, dosage modifications and method of administration

N.a.

5.7 Preparation and labelling of Investigational Medicinal Product

N.a.

5.8 Drug accountability

N.a.

6. NON-INVESTIGATIONAL PRODUCT

N.a.

6.1 Name and description of non-investigational product(s)

N.a.

6.2 Summary of findings from non-clinical studies

N.a.

6.3 Summary of findings from clinical studies

N.a.

6.4 Summary of known and potential risks and benefits

N.a.

6.5 Description and justification of route of administration and dosage

N.a.

6.6 Dosages, dosage modifications and method of administration

N.a.

6.7 Preparation and labelling of Non Investigational Medicinal Product

N.a.

6.8 Drug accountability

N.a.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

Primary outcome is the proportion of undertreatment and overtreatment discovered and reduced by medication review.

7.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcome measures are:

- Proportion of medication related readmissions within a period of 6 months before and after the index visit to the ED
- Costs associated with the intervention (labour costs pharmacist; costs of readmissions, costs of overtreatment).
- Quality of life, as measured with Eq5D questionnaire at time of hospital/ED discharge and 6 months after discharge
- Proportion of ED visits recognised as being caused by a medication related problem.
- The experience of patients on the interventions of the ED-pharmacist, evaluated with interviews.

7.1.3 Other study parameters (if applicable)

General patient characteristics (age, gender, renal function, length of hospital stay, number of medicines chronically used, all medication in use [medication history from the community pharmacy: 6 months before ED visit and 6 months after], type of medication related problem causing the ED visit, all other types of medication related problems detected by the medication review, communication of medication related problem in discharge letter, transfer of this discharge letter information to the community pharmacy record.

Percentage of pharmacist advices regarding under- and overtreatment and regarding other issues identified by the medication review that is accepted by the prescriber.

7.2 Randomisation, blinding and treatment allocation

N.a. (non-blinded, non-randomised, within subject before-after study).

7.3 Study procedures

First, during 3 months the ED pharmacist will be implemented on the ED.

Each included patient will have 6 months follow-up after discharge (medication history, quality of life questionnaire, hospital readmissions). For each included patient we will also look back for 6 months and collect medication histories (for assessment of over- and undertreatment before the intervention) and medication related hospital admissions.
Interviews with 10 patients who provide informed consent will be carried out approximately two weeks after discharge to evaluate the experience and perspective of patients on the ED-pharmacist intervention. A psychology student will visit patients at home. The interview contains open and semi-structured questions and will take about 40 minutes. The interview will be recorded.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason without any consequences.

7.4.1 Specific criteria for withdrawal (if applicable)

N.a.

7.5 Replacement of individual subjects after withdrawal

Regarding the interviews with 10 patients, the subjects who leave the study will be replaced.

7.6 Follow-up of subjects withdrawn from treatment

N.a.

7.7 Premature termination of the study

N.a.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

The reporting of AEs, SAEs and SUSARs is not needed in this study, as it does not concern a medication trial and as it is not 'WMO-plichtig'.

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

< Please describe the procedures for handling the serious adverse events. If certain SAEs do not require immediate reporting by the investigator to the sponsor, please specify.>

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs: not applicable <*specify which SAEs do not require immediate reporting by the investigator to the sponsor, if applicable*> .

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

< *If certain SAEs do not require(expedited) reporting to the accredited METC, please specify these SAEs as well as the frequency of reporting of these SAEs in line listings, or in a annual safety report or otherwise.>*

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

<This c*hapter is only applicable for studies with an investigational medicinal product*>

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal

ToetsingOnline to the METC *<reporting via webportalToetsingOnline is only applicable for investigator initiated studies>*:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

< For multicentre studies the responsibilities of investigators in participating centres as well as of the coordinating investigator should be clearly defined>

<Please describe also the method of breaking the code for SUSAR reporting.>

8.3 Annual safety report

<This c*hapter is only applicable for studies with an investigational medicinal product>*
< The annual safety report may be combined with the annual progress report (see chapter 12.4).>

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

8.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

N.a.

9. STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

The difference in the proportion of under- and overtreatment as assessed by STOPP-START criteria between both periods is analysed by the McNemar test (paired analysis of dichotomous variables). Odds ratios and 95% confidence intervals are reported.

9.2 Secondary study parameter(s)

The difference in the proportion of medication related readmissions between both periods is analysed using the McNemar test. The difference in quality of life score is analysed using the paired t-test.

Cost effectiveness is calculated from a healthcare perspective.

The difference in the experience of patients on the interventions of the ED-pharmacist is qualitatively analysed.

9.3 Other study parameters

N.a.

9.4 Interim analysis (if applicable)

N.a.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. This study does not fall within the scope of WMO.

10.2 Recruitment and consent

Patients will be asked consent in order to retrieve their medication histories and information on readmissions, and in order to send them the quality of life questionnaire 6 months after the ED visit.

10.3 Objection by minors or incapacitated subjects (if applicable)

N.a.

10.4 Benefits and risks assessment, group relatedness

N.a.

10.5 Compensation for injury

N.a.

10.6 Incentives (if applicable)

N.a.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

All data will be coded, with the key to the code kept separate from the data. Data thus collected will be stored in Open Clinical, complying with GCP guidelines.

11.2 Monitoring and Quality Assurance

Data monitoring will take place at the end of the before period (check on truly existing patients, validity checks on entered data) and again at the end of the after period (same checks).

11.3 Amendments

N.a.

11.4 Annual progress report

N.a.

11.5 Temporary halt and (prematurely) end of study report

N.a.

11.6 Public disclosure and publication policy

N.a. Study data will be used for one or more peer reviewed publications.

12. STRUCTURED RISK ANALYSIS

N.a.

12.1 Potential issues of concern

N.a.

a. Level of knowledge about mechanism of action

N.a.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

N.a.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

N.a.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

N.a.

e. Analysis of potential effect

N.a.

f. Pharmacokinetic considerations

N.a.

g. Study population

N.a.

h. Interaction with other products

N.a.

i. Predictability of effect

N.a.

j. Can effects be managed?

N.a.

12.2 Synthesis

N.a.

13. REFERENCES

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