S1 Appendix

Contents

ORIGINAL TRIAL PROTOCOL

English title:

Effect of a Pharmacist Intervention on Hospital Readmissions

A project at the Internal Medicine Ward, the Medical Clinic, Oslo University Hospital, Norway, in cooperation with Hospital Pharmacies Enterprise, South-Eastern Norway Regional Health Authority and University of Oslo, Norway

Study protocol version number 1 – 07-04-2014

Project members

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Abstract

Several Norwegian studies have shown that pharmacists working in multidisciplinary treatment teams solve and prevent drug-related problems (DRP). Studies investigating the effect of pharmacist interventions on clinical relevant outcome measures are however lacking. Readmissions have both negative clinical and economic consequences, and time to the first readmission is considered as a clinical relevant outcome measure. The main aim of the current study is to investigate the effect of a pharmacist intervention, on patients` time to the first hospital readmission. The study is carried out as a randomised controlled, unblinded study. In total, 400 patients will be included.

Patients acutely admitted to the internal medicine ward at Oslo University Hospital, Ullevaal, using a minimum of 4 regular drugs from a minimum of 2 therapeutic classes (ATC level 1), will be enrolled in the study following written informed consent. The patient inclusion period starts in August 2014, and will last until the target number of patients have been included, estimated to approximately one year.

A “baseline assessment” will be conducted by a pharmacist for all included patients, consisting of medicines reconciliation and review at hospitalization, to measure frequency of DRPs at admission. Retrospectively, an assessment of whether DRPs may have led to the hospitalisation will be conducted, by comparing possible consequences of the DRPs with the admission cause.

Following the baseline assessment, the patients will be randomized to the control- or intervention group. Patients in the control group will receive in-hospital standard care, i.e. without pharmacist involved. Patients in the intervention group will receive a pharmacist intervention comprising inclusion of a pharmacist in the multidisciplinary treatment team during the hospital stay. The pharmacist will conduct medication reconciliation at admission, perform medication reviews during the hospital stay and provide drug information (written and oral) to the patient before discharge, as well as written drug information to the next level of care.

The main outcome measure is difference between the control- and intervention groups in time to the first readmission, in the intention-to-treat population. Data on readmissions will be retrieved from the Norwegian Patient Registry.

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Abbreviations:

ATC	Anatomical Therapeutic Chemical
CIRS	Cumulative Illness Rating Scale
DRP	Drug-related problem
IMM	Integrated Medicines Management
ITT	Intention to treat
MAI	Medication Appropriateness Index
NPR	Norwegian Patient Registry
REK	Regional ethics committee
UIO	University of Oslo

Introduction

The individual patient`s drug therapy steadily becomes more complicated (1). It has been estimated that more than half of the drugs prescribed are used inappropriately, and 5-10% of admissions to internal medicine hospital wards can be attributed to inappropriate use of drugs (1). Inappropriate drug use has both clinical and economic consequences and "the Norwegian`s" Medicines Agency have estimated that direct cost of hospital admissions caused by adverse drug reactions equals 300-400 million annually (1).

A significant proportion of the medication errors appear at transition points between care levels, due to missing or uncomplete information provided during transition. At hospital admission, errors in the drug lists have been reported in 85-95 % of patients (2, 3). Furthermore, up to 40% of hospitalizations in the elderly are known to be caused by adverse drug reactions, whereof the majority could be avoided (4, 5).

Pharmacists may contribute in multidisciplinary treatment teams in hospitals by tailoring and optimizing patients' drug therapy during hospitalizations, and preventing drug errors at transition points between different levels in the healthcare system (6, 7). In Norway, several studies have shown that pharmacists solves and prevent DRPs when working in multidisciplinary treatment teams in hospitals (8-10), but studies investigating the effect of such interventions on clinical relevant outcome measures is lacking. Readmissions is perceived as a burden to both patients and their relatives, in addition to being resource demanding to the society. Time to the first readmission is therefore considered as a clinical relevant outcome measure.

The internal medicine ward in the Medical Clinic at Oslo University Hospital, Norway, comprises 24 beds, and have around 100 patient admissions per month according to the annual report of the Medical Clinic, Oslo University Hospital. The patients are often multimorbid and use many drugs. The most common reasons for hospitalization are deep vein thrombosis, pulmonary embolism, diabetes and pneumonia. Due to its patient population, the internal medicine ward is a suitable place to conduct the present study.

Aim

The main aim of this study is to investigate the effect of a pharmacist intervention on the patients` time to the first hospital readmission.

Methods

- *Study design*
  Randomized controlled, unblinded, intervention study

- *Study location and –period*

  The study will be conducted at the internal medicine ward, Oslo University Hospital, Ullevaal location, Norway. Patient inclusion will start autumn 2014, and last until the target number of patients are included. The goal is to include the target number of patients within one year. The follow-up will last for 12 months after discharge for readmissions and contact with emergency rooms, by data from the Norwegian Patient Registry, and mortality, by data from Statistics Norway.

- *Inclusion criteria*

Adult women and men acutely admitted to the internal medicine ward, using a minimum of 4 regular drugs from a minimum of 2 therapeutic classes (ATC level 1) before medicines reconciliation – the latter as a surrogate for the number of diagnoses. If it is revealed during medicines reconciliation that a patient was using less than 4 regular drugs from less than 2 therapeutic classes (ATC level 1) before hospitalization, the patient will be excluded from the study.

Exclusion criteria

- Terminally ill patients
- Patients not able to communicate in Norwegian language or English
- Patients who do not want to participate in the study
- Patients previously included into the study, will not be re-included during their second admission to the general internal medicine ward, neither receive the study intervention during this second hospitalization

- *Number of patients that will be included*
  Readmission frequencies in earlier studies in Ireland and Sweden, as well as Oslo University Hospital , is estimated to approximately 50% in a year. To be able to detect a 15% absolute reduction in readmissions, with 80% power, 168 patients must be included to both treatment groups. To account for dropouts, 200 patients will be included to both the control and the intervention groups.

- *Randomization procedure*
  Following inclusion, patients will be allocated by a randomization sequence with a permuted block design, to the control- or intervention group. The Centre for Biostatistics and Epidemiology, Oslo University Hospital, Norway, is responsible for the randomization procedure and will deliver allocation envelopes. Study pharmacists will conduct the inclusion according to the randomizing procedure, for all included patients.

- *Flow chart and description of study arms:*

  Figure 1 shows the flowchart for the study, including a description of when the different steps in the study should be conducted

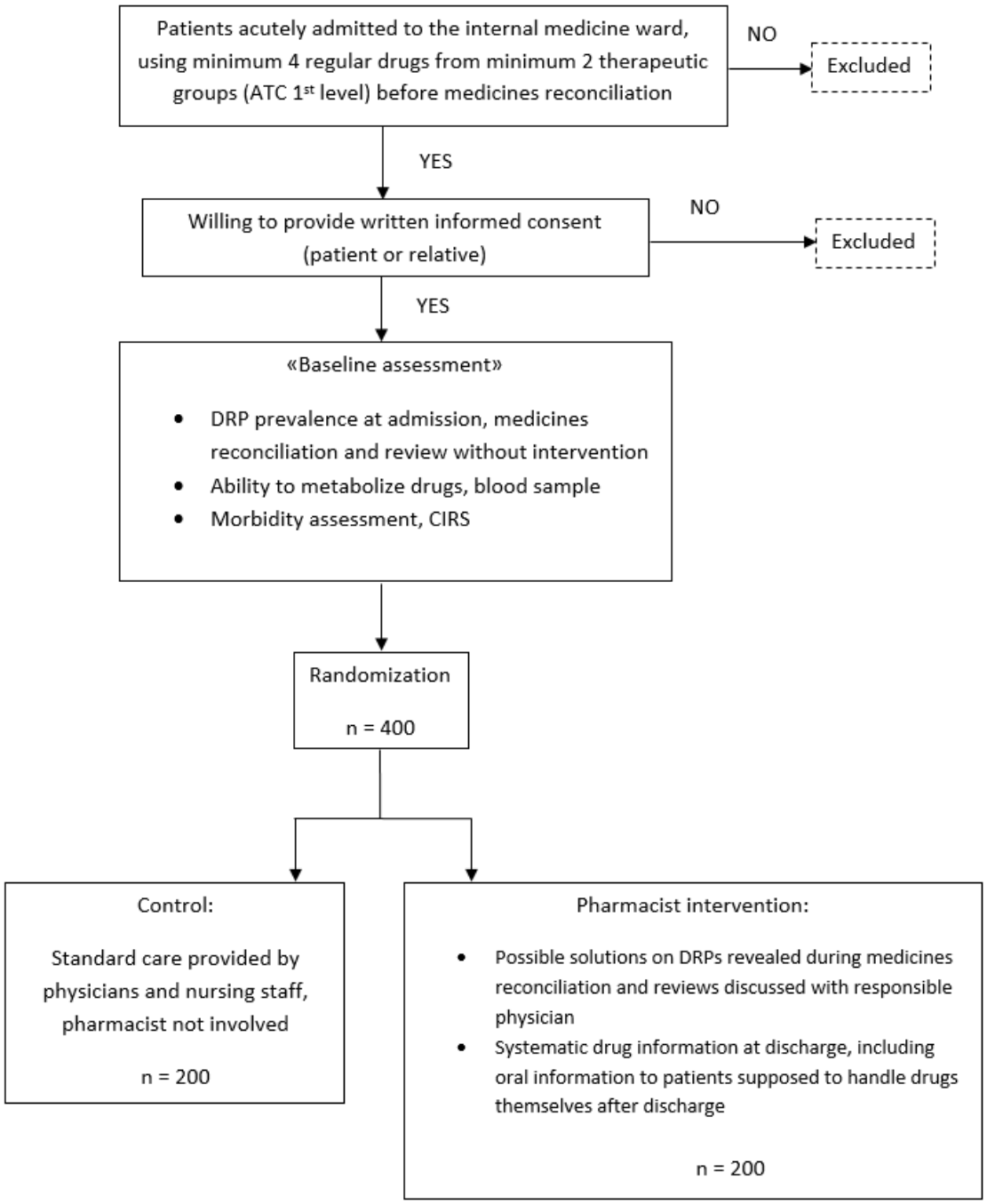

Figure 1. Overview over how the study will be conducted.
ATC = Anatomical Therapeutic Chemical, DRP = drug-related problems, CIRS = Cumulative Illness Rating Scale.

”Baseline assessment”

For all included patients, a «baseline assessment» will be conducted, consisting of three steps:

- Assessing the DRP prevalence at at admission, by conducting medicines reconciliation and –review
- Assessing the patients` ability to metabolize drugs, as determined from a blood sample
- Assessing the patients` morbidity, by using the standardized method Cumulative Illness Rating Scale (CIRS)

The ”baseline assessment” will be conducted before the randomization, to avoid data collection bias.

For all included patients, a blood sample (full blood) will be sent to Center for Psycopharmacology at Diakonhjemmet Hospital, and analysed for the patient`s ability to metabolize drugs. The blood sample will be drawn as a part of standard blood tests at hospitalization. It will be investigated whether congenital variation in the ability to metabolize drugs correlates with DRP and/or morbidity. By comparing possible consequences of DRP at hospitalization, it will be investigated whether DRPs may have caused the hospitalization. A group of physicians and pharmacists will conduct these assessments in collaboration.

Control group and intervention group

Patients randomized to the control group will receive standard care at the internal medicine ward, provided by physicians and nursing staff, without pharmacist involved. If a physician should request pharmacist advice regarding a patient randomized to the control group, a pharmacist will deliver this, and the patient will be excluded from the study.

Patients randomized to the intervention group will receive pharmacist intervention in addition to standard care during the hospital stay. This comprises inclusion of a pharmacist in the multidisciplinary treatment team around the patients, conducting the following tasks:

1) Discussion with physician responsible for the patient regarding possible solutions on DRPs revealed at baseline (admission) by medicines reconciliation (11) and review (12). Medicines review will be conducted repeatedly at changes in drug therapy or the patient`s clinical state.
2) Drug information at discharge will be written by a template where all changes in the patient’s drug list during the hospital stay will be systematically described and justified. The drug information will be approved by the hospital physician responsible for the patient’s treatment and delivered to the patient and the next care level at hospital discharge.
3) Oral drug information before discharge, where the aim is to improve the patient`s adherence, for patients supposed to handle drugs themselves after discharge.

Procedures and training

The Hospital Pharmacies Enterprise's procedures for the conduct of medicines reconciliation and review will be followed during the conduct of these tasks (11, 12). The procedures are based on the "Integrated Medicines Management" (IMM)- model, for clinical pharmacists, developed in Northern Ireland (6, 13) and further developed in Sweden (14) and Central Norway (15). When working according to this model, the pharmacists' continuous and systematic evaluation of the patient`s drug treatment at hospital admission (medicines reconciliation), during the hospital stay (medicines review) and at discharge (systematic drug information) is ensured. Procedures and forms are used during each step of IMM.

Medicines reconciliation involves the identification of a complete and accurate list of drugs currently in use by a patient, by using different and the most optimal sources of information, including the patient, their next of kin, home care nurse, nursing home staff, pharmacy and/or general practitioner. Medicines discrepancies between drugs prescribed at hospitalization and the complete drug list, are revealed. Medicines review is a systematic review of a patients` drug treatment, using a checklist of risk categories, where the drugs` effect, safety and indications are evaluated. Potential and manifested DRPs are revealed.

DRPs revealed in patients who, following the baseline assessment are allocated to the control group, will not be discussed with the physician responsible for the patient's treatment, unless they are considered by the pharmacists as being of major clinical relevance, i.e. that they may cause detrimental effects or death. If the pharmacist is in doubt regarding the severity of a DRP, the decision will be taken by the project leader Dr. nn, or the medical responsible senior physician at the internal medicine ward, nn. If DRPs with severe clinical relevance are revealed in patients allocated to the control group, they will be discussed with the ward physician responsible for patient treatment, and the patient will be excluded from the study.

Clinical pharmacists conducting the pharmacist intervention in the study shall attend and get approval of training in the different working methods;

- Three day theoretical course in medicines reconciliations and reviews by IMM, followed by practical training including feedback on their individual performance provided by a clinical supervisor.
- The course "From monologue to dialogue – communicating with patients in theory and practice", comprising theoretical and practical training in talking with patients about drugs, with feedback from a supervisor.

- *Demographic data and measurements*

The following demographic data and measurements will be registered for the study population:

- ✓ Age
- ✓ Sex
- ✓ Cause of hospitalization
- ✓ Diagnoses according to ICD-10, as described in the patient's medical record, i.e. diagnoses in the epicrisis, and in addition other diagnoses clearly

described in the medical record during the hospital stay, but not listed in the epicrisis.

- ✓ Where the patient is admitted from (home, other hospital, other hospital ward in the same hospital, nursing home, emergency room, general practitioner, municipal emergency room, others)
- ✓ Assistance with handling of drugs prior to admission: nursing home, home nurse, multidose dispensed drugs, patients handling drugs themselves or not
- ✓ Hospital admission date
- ✓ Internal medicine ward admission date
- ✓ Date for last hospitalization (from the Norwegian Patient Registry)
- ✓ Date for medicines reconciliation and review conducted by pharmacist
- ✓ Drug list documented at hospital admission, including over-the-counter drugs, natural/herbal drugs (when documented). Drug name, strength, dosage, formulation (e.g. injection, rectal, oral) and time of dose.
- ✓ Drug list obtained by pharmacist, including over-the-counter drugs and natural/herbal drugs. Drug name, strength, dosage, formulation (e.g. injection, rectal, oral) and time of dose.
- ✓ Source(s) used during the medicines reconciliation (nursing home, general practitioner, multidose delivering pharmacy or next of kin)
- ✓ Drug treatment during the hospital stay
- ✓ Number and type DRPs revealed by medicines reconciliation and review, if the DRPs are discussed with the ward physician responsible for the treatment or not, and eventual results of such discussion
- ✓ Discharge date
- ✓ Where the patient is discharged to (home, other hospital, other ward at the same hospital, nursing home, others)
- ✓ Drug list at discharge. Drug name, strength, dosage, formulation (e.g. injection, rectal, oral) and time of dose.
- ✓ Results from the blood test, ability to metabolize drugs
- ✓ Morbidity at hospitalization, by using Cumulative Illness Rating Scale (CIRS)

The primary endpoint is difference between the control and intervention group in time to the first readmission, for the intention-to-treat-population. Data on readmissions will be obtained from the Norwegian Patient Registry.

Differences in clinically relevant outcome measures will be investigated between patients receiving the pharmacist intervention (intervention group) and patients not receiving pharmacist intervention (control group). Secondary endpoints will include:

- ✓ Number of readmissions during 30 days, 6 months, 12 months
- ✓ Proportion of patients readmitted during 30 days, 6 months and 12 months after discharge
- ✓ Number of contacts with emergency rooms during 30 days, 6 months and 12 months after discharge
- ✓ Proportion of patients in contact with emergency rooms during 30 days, 6 months and 12 months after discharge

- ✓ Number of days to the first readmission
- ✓ Length of stay (days) during the first readmission
- ✓ Number of days to contact with emergency room
- ✓ Mortality: Proportion of patients who dies in the 12 months after discharge
- ✓ Difference in Medicines Appropriateness Index (MAI)-score (16) from admission to discharge
- ✓ Quality of discharge drug information
- ✓ Difference in DRP prevalence (number and type of DRPs) at hospitalization
- ✓ Difference in morbidity (CIIRS) at hospitalization

Further, any difference in "DRP -load" and morbidity (CIRS) at hospitalization will be investigated in patients hospitalized compared to those not hospitalized during the last 6 months before index admission. Any possible causal relationship between DRPs and hospitalizations will be assessed. Congestinal variations in ability to metabolize drugs will be assessed against "DRP-load" and/or morbidity.

The number of phone calls after discharge from the next care level to the internal medicine ward, will be measured by statistical process control (SPC).

Outcome measures including readmissions, emergency room contacts and mortality will be registered in the control- and intervention group at three points of time: 30 days, 6 months and 12 months after discharge. All cause readmissions will be registered. The main cause of readmission or contact with the emergency room will be registered. Data on readmissions and emergency room contacts will be obtained from NPR. Data on mortality will be obtained from Statistics Norway, after necessary permissions from the State Health Authority and the The Norwegian Data Protection Authority are obtained.

- *Privacy policy and information*

  Patients will be enrolled following written informed consent. The physician responsible for the patient's treatment at the hospital decides whether the patient is competent to consent or not. Written informed consent will be obtained from next of kin for patients who are not competent to consent. After written consent is obtained, the patient will be provided a study number. The enrolled patients will have the right to withdraw their consent at any time point, without giving any explanation. The participants will receive a copy of the informed consent. The information leaflet will describe that participation in the study includes extraction of data from the Norwegian Patient Registry and Statistics Norway during the first year after hospital discharge. The signed consents will be stored in a locked cabinet at the hospital together with the code list.

- Processing and storage of data

All data will be handled confidentially and personal, identifiable data will not be taken out of the hospital. The data will be processed without patient names or personal identification numbers, after each participant has been given a study number. The code list linking the study number to the

personal identification number, will be stored in a locked cabinet at the hospital, separately from other data. The code list will be shredded August 2018 at latest. Signed informed consents will be stored together with the code list. Study forms (paper) will be stored without patient names or personal identification numbers, in a locked cabinet and unavailable for unauthorized persons. Electronic data files will be stored without patient names or personal identification numbers, and processed in a research database at Oslo University Hospitals research server.

- *Definition of analysis population*

An Intention-to-treat (ITT) analysis will be conducted. All randomized patients will be included in the analysis. Patients lost to follow-up will be included in the analysis as «not readmitted», «not had contact with emergency rooms». A per protocol analysis will also be conducted. Patients dying during the study period will only be included in mortality analysis.

Ethics and safety

The study hypothesis is that pharmacists' care in the intervention group, will lead to increased quality of drug treatment compared to the control group, and that this may be reflected by reduced risk of hospital readmission after discharge. There might be a risk of lower quality drug treatment in the intervention group. We consider the probability of this to be low.

Pharmacists' care during a hospital stay is not included in standard care today. Patients in the control group will therefore be provided with the same care during their hospital stay, as they would have been provided with if they did not participate in the study. All included patients will have a conversation with a pharmacist and a blood sample will be drawn, which is not considered to cause any disadvantage to the patients. The blood sample will be drawn as a part of the samples taken due to hospitalization. Before patients are enrolled, the will receive an information leaflet of the study and they will themselves decide whether they want to participate or not.

To document the effect of clinical pharmaceutical intervention in Norwegian hospitals is necessary, and randomized controlled trials are the gold standard. On this basis, it is considered necessary to randomize to a control group receiving standard care, i.e. without pharmacist involved. During standard care at the internal medicine ward, no patients receive pharmacist intervention the way it is planned conducted in the study. This means that it makes no difference for patients in the control group, whether the study is conducted or not. If potentially severe DRPs are revealed after hospitalization, they will be discussed with the responsible ward physician, and the patient will be excluded from the study. If a physician at the general internal medicine ward request a pharmacist`s opinion in some degree to patients allocated to the control group, this will be provided, and the patient will be excluded from the study. In this way, the safety of patients in the control group is secured, and we hence consider the study as ethical acceptable.

A biobank will be established, called «blood samples for analysis of drug metabolizing enzymes». The project leader is responsible for the biobank. Blood samples will be marked with the patient`s study number and locked in and separated from the code list connecting patient identity to study number.

The blood samples will be transported by a project group member from the ward at Oslo University Hospital to Center for Psycopharmacology at Diakonhjemmet Hospital, where the analysis will be conducted.

All collected data will be handled confidentially and personal identifiable data will not be taken out of the hospital. The data will be processed without patient identification, with a study number per patient. The code list connecting patient identity to study number will be locked in at the hospital and separated from other data. The code list will be deleted December 31th 2018 at the latest. Signed informed consents will be stored locked in, together with the code list. Paper versions of data registration forms will be without patient identification and stored locked in and not available for unauthorized persons. Electronical data without patient identification will be stored and processed in a research database, stored at Oslo University Hospital`s research server.

Approvals from Regional committees for medical and health research ethics (REK) and the Personal Ombudsman will be obtained. For retrieval of data on mortality from Statistics Norway will necessary approvals be obtained from the State Health Authority and the The Norwegian Data Protection Authority.

There is no conflicts of interests by conducting the study.

Statistics

Demographics will be presented as proportions, means with standard deviations or medians with ranges. The primary endpoint (time to first readmission) will be estimated using Kaplan Meier analysis and the groups will be compared by log rank test. The frequency endpoints will be analysed by chi square tests. Continuous variables will be analysed with Mann-Whitney tests or t-tests. A significance level at 5% will be used.

Time Schedule

Spring 2014: Complete study protocol, clarify collaborators

By April 8th 2014: Application to Regional committees for medical and health research ethics

March to August 2014: Necessary training provided to clinical pharmacists

May to June 2014: Develop and complete databases and data collection forms

August 2014: Data inclusion start, assumed duration of patient inclusion approximately 1 year, then 1 more year before data on readmissions can be retrieved

August 2015 to December 2016: Data processing, data analysis, prepare papers

Spring 2017: Write PhD thesis

Autumn 2017: Submit and defend PhD thesis

Budget

The project is assigned a PhD grant, 4 years 75% position, from South-Eastern Norway Regional Health Authority, project number 2013055. In addition, an 80% pharmacist position, funded by Oslo University Hospital and the Medical Clinic will be used into the project.

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PROTOCOL AMENDMENTS

June 16th 2014

Amendment to "Inclusion criteria": To count the number of drugs from different ATC groups, all drugs marked as "used before hospital admission", i.e. marked with"→" on the paper medical record, either by physicians at the internal medicine ward or at another hospital ward which the patient is transferred from, should be included. If the patient is transferred from another hospital ward where drugs used before hospital admission clearly are not written on the paper medical record, e.g. the intensive care unit, number of drugs described in the electronical admission record, should be counted.

August 15th 2014

Amendment to "Inclusion criteria":

- The patient must have a Norwegian personal identification number (to be able to retrieve readmission data from the Norwegian Patient Registry)

Amendments to "Exclusion criteria":

- Patients isolated due to severe infections
- Patients with temporary lack of consent due to acute illness, assessed by the responsible ward physician. If the patient have not handled their drugs themselves before hospitalization, and consent can be retrieved from the patients next of kin, the patient may be included.

June 7th 2016

Charlson comorbidity index (CCI) score will be used as the morbidity measure, instead of CIRS.

April 10th 2017

The data collected in the study will be used in additional analysis. The aim is to investigate which patients who will benefit most of the pharmacist intervention, and which patients that have the highest risk of hospital readmissions. We will also investigate the importance of the different components of the intervention. Data from all included patients in both the intervention and the control group will be used to investigate significant explanatory variables for the risk of readmissions.

Candidate variables will consist of both clinical and drug-related variables. A Cox regression analysis will be conducted, with "time to first readmission or death" as dependent variable.

Candidate variables will be:

- Age
- Sex
- Kidney function
- Pharmacogenetic variability in drug metabolizing enzymes
- If the patient is admitted from or discharged to a nursing home or home nurse care
- If the patient receives multidose dispensed drugs

- Length of hospital stay
- Charlson Comorbidity Index?
- Diagnoses, e.g.
    - Lung diseases
    - Heart failure
    - Coronary disease
    - Malignant disease
    - Dementia
- Drug related variables
    - Number of drugs at hospital discharge
    - Drugs in different ATC groups

The modelling will start with univariate analysis of all variables which may be associated with time to first readmission. Explanatory variables with p values < 0.2 will be included in the multivariate analysis. Dependant on the number of explanatory variables to be included in the multivariate analysis, the variables in the final model will be decided by 1) forward inclusion of one and one variable or 2) backwards elimination of one and one variable, until the model consists of only statistically significant variables.

To investigate if subgroups of patients have increased effect of the intervention, an interaction term will be added to the model, the same way as described above.

The model will be validated with data collected in a new cohort of patients from the internal medicine ward and from observational data from other internal medicine wards at hospitals in the South-Eastern Norway Regional Health Authority.

The study is approved with end-date October 31th 2017, and storing of data until October 31th 2022. Due to the planned additional analysis, new end-date will be January 1th 2020, and data will be stored until January 1th 2025.

May 22th 2018

According to the original protocol mortality outcome data would be retrieved 12 months after index hospital discharge for each patient. Since the inclusion period lasted 1.5 years, followed by time spent on developing of the research database, we were unable to conduct data analysis before now. The first patient was enrolled August 2014, the last March 2016. Follow-up regarding mortality will be extended to December 31th 2017 for all included patients, to increase statistical power.

June 26th 2018

According to the original protocol readmission outcome data would be retrieved 12 months after index hospital discharge for each patient. Since the inclusion period lasted 1.5 years, followed by time spent on developing of the research database, we were unable to conduct data analysis before now. The first patient was enrolled August 2014, the last March 2016. Follow-up regarding readmissions will be extended to December 31th 2017 for all included patients. The primary endpoint will however not be changed, but remain as detailed in the statistical analysis plan which was signed May 25th 2018.

Statistical analysis plan – Oslo pharmacist intervention study - effect on readmissions (OPERA)

1. Introduction

The aim of this study is to investigate the effect of an in-hospital pharmacist intervention in multimorbid patients using at least four drugs. The study is registered in Clinicaltrials.gov (NCT02336113). Some basic elements from the study protocol are recapitulated below. The aim of this document is, prior to the conduction of analysis, to establish a detailed plan for statistical analysis, beyond what is written in the protocol.

Inclusion and exclusion criteria

Inclusion criteria were age ≥ 18 years, Norwegian citizen, unplanned hospitalization, and use of a minimum of four regular drugs at admission. The drugs were required to represent a minimum of two Anatomical Therapeutic Chemical (ATC) groups [1] at 1st level to enrich the inclusion of multimorbid patients.

Patients who were i) terminally ill, ii) isolated due to severe infections or iii) unable to communicate in Norwegian or English and in lack of an interpreter, were excluded. Patients readmitted during the study period were not eligible for a second inclusion. Patients, for whom medicines reconciliation revealed use of less than four regular drugs at admission, were excluded.

Randomization and blinding

The patients were randomized 1:1 to usual care or pharmacist intervention. Staff at the Centre for Biostatistics and Epidemiology, Oslo University Hospital, was responsible for the randomization procedure. This staff had no contact with the patients, study pharmacists or ward staff. A permuted block randomization was generated and delivered to the study pharmacists in sequentially numbered, opaque, sealed envelopes. Investigators were blinded to block size. In order to minimize the risk of selection bias, the randomization took place after patient inclusion, after baseline assessments were conducted. The randomization envelopes were drawn by one of the study pharmacists after controlling that the envelope with the lowest number was used.

It was not feasible to blind the patients or the study pharmacists. Nor was it feasible to blind ward staff to which patients were allocated to the pharmacist intervention group. The ward staff were however not informed of which patients that were control patients in the study. Data on readmissions were provided by The Norwegian Patient Registry and data on deaths were provided by The Norwegian Cause of Death Registry, by staff blinded for group allocation.

Primary endpoint

The primary endpoint is difference between the patient groups in time to the first unplanned hospital admission or death within 12 months after index stay discharge.

Secondary endpoints

Secondary endpoints are differences between the patient groups in:

- Time to the first unplanned readmission within 12 months after index stay discharge (censored for deaths)
- Number of unplanned and planned readmissions per patient, within 30 days, 6 months and 12 months after index discharge
- Proportion of patients unplanned hospitalized within 30 days, 6 months and 12 months after index discharge
- Proportion of patients dead or unplanned hospitalized within 30 days, 6 months and 12 months after index discharge
- Proportion of patients dead within 30 days, 6 months, 12 months and 20 months after index discharge
- Length of hospital stay of the first unplanned readmission
- Total mortality, from index discharge date until 31.12.2017
- Change in Medicines Appropriateness Index (MAI)-score [2] from index hospital admission to index hospital discharge
- Quality of drug discharge information at index hospital discharge

Some of the secondary endpoint analyses may be published in separate papers.

Background variables

The following background variables have been collected:

- Age
- Sex
- Reason for admission
- Medicine administration assistance prior to admission, and after discharge, i.e. receiving drugs from a home care nurse
- Living situation prior to admission, and after discharge, i.e. living at home or at a nursing home
- Diagnoses (ICD-10)
- Charlson Comorbidity Index Score [3]
- Last hospital admission, up to 6 months prior to index stay
- Date for index hospital admission and discharge, hence length of index stay
- Drugs prior to admission, during hospital stay and at hospital discharge, including posology
- Drug-related problems at baseline for all included patients
- Drug related problems during hospital stay for intervention patients
- Genetic variability in drug metabolizing enzymes
- Body-mass index
- Glomerular filtration rate
- Serum-albumine
- C reactive protein (CRP)

Power calculation

The sample size calculation was based on a previous study on a similar patient population reporting a readmission frequency of 50% in 12 months [4], as well corresponding readmission frequencies for patients discharged from the internal medicine ward (information from South-Eastern Norway Regional Health Authority). It was estimated that to detect a 15% absolute reduction in hospital readmissions with 80% power and a significance level of 5%, we would require 168 patients in each group. To compensate for any drop outs a total of 200 patients in each group were enrolled in the study.

Since a survival analyse utilizes the information better than a comparison of proportions at a given time, the power will be somewhat higher than estimated above.

Patient flow

Patient flow is illustrated in Figure 1. Figure 2 shows a further description of the 200 patients allocated to the pharmacist intervention group.

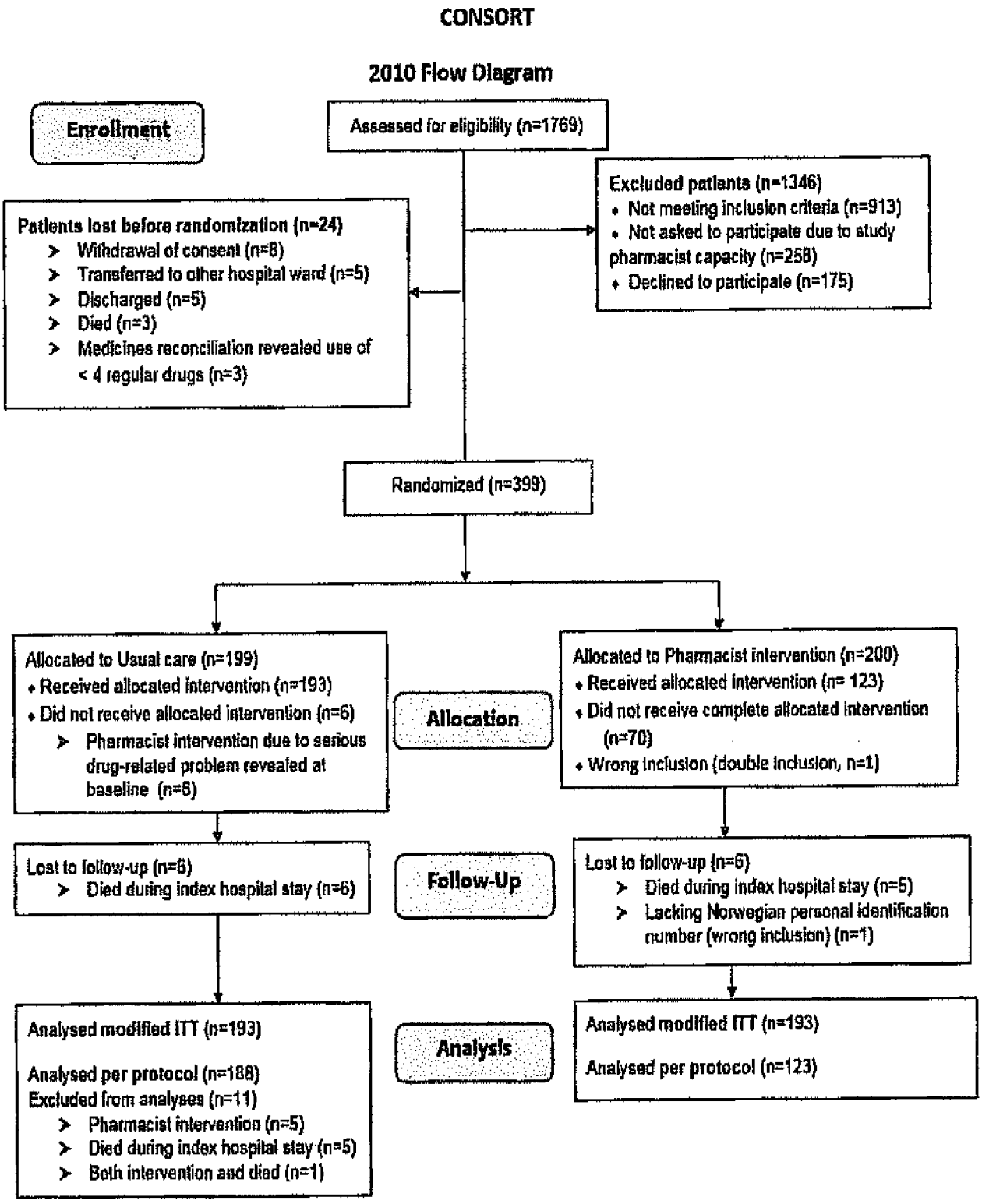
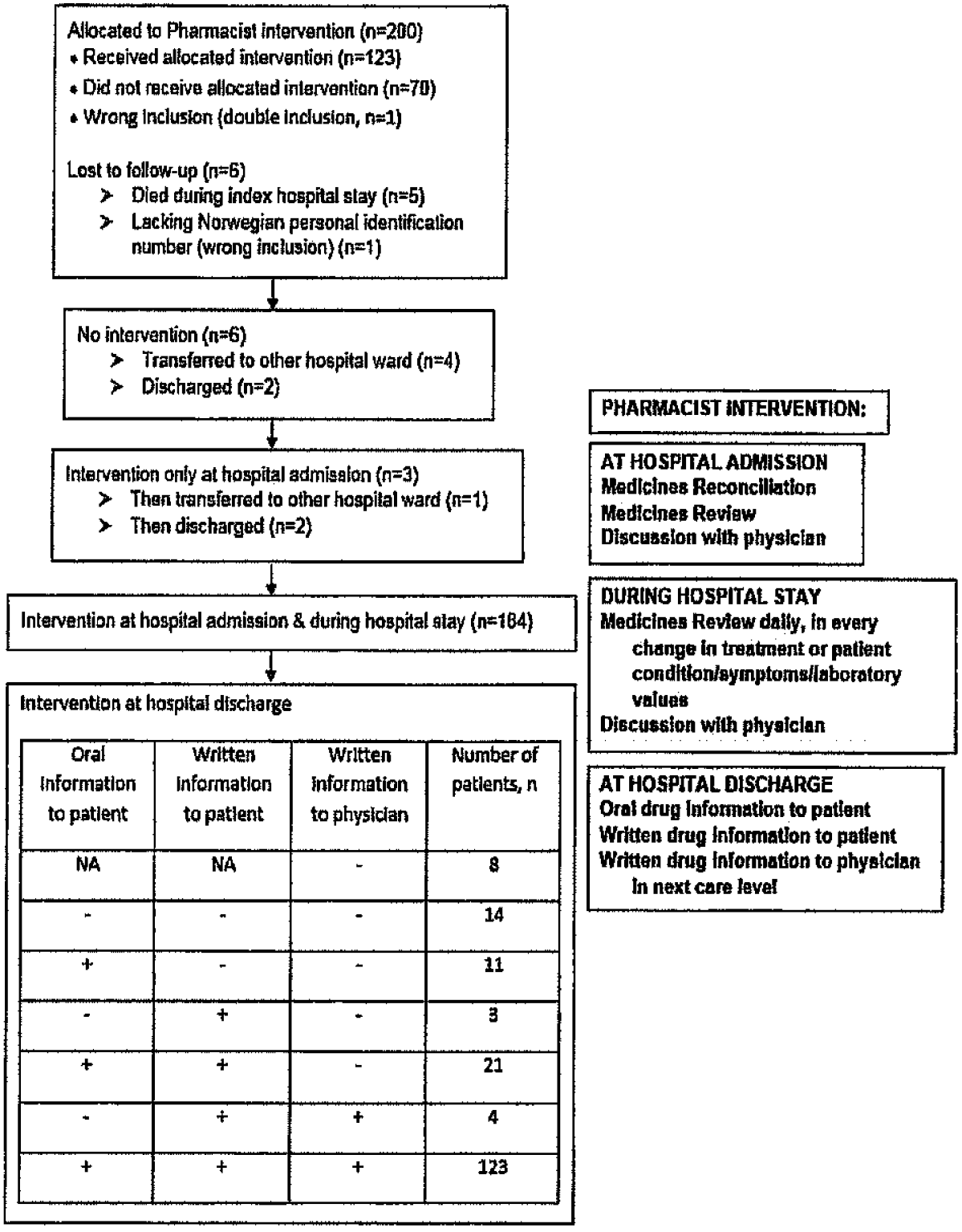


Figure 1. Patient flowchart. ITT = intention to treat.



Oral information to patient	Written information to patient	Written information to physician	Number of patients, n
NA	NA	-	8
-	-	-	14
+	-	-	11
-	+	-	3
+	+	-	21
-	+	+	4
+	+	+	123

Figure 2. Flowchart further describing the patients allocated to the pharmacist intervention group. NA = not applicable.

Definition of analysis populations

The primary efficacy analysis is a modified intention to treat (MITT):

- Patients who died during the index hospital stay were excluded because they never were discharged and at risk for hospital readmissions or death after discharge.
- One patient was lost to follow up due to a lack of Norwegian personal identification number (wrong inclusion) and was excluded.
- One patient was wrongly included, in terms of being a readmitted patient, already included in the study. The second, wrong inclusion, was excluded. The patient is included in the analysis using data related to the first admission.

A per protocol (PP) analysis consists of patients that received the complete allocated intervention:

- In the control group, for patients with drug related problems revealed at baseline suspected to cause detrimental effects or death if not acted upon, the study pharmacist intervened. These patients were excluded.
- In the pharmacist intervention group, all patients receiving none or only parts of the predefined intervention were excluded.

2. Primary endpoint analysis

The primary endpoint analysis will be done at the MITT population.

The primary endpoint analysis is a time-to-event analysis. The Kaplan Meier method and the log-rank test will be applied. Further, a Cox proportional hazards model will be applied to estimate hazard ratios. A p value below 0.05 will be regarded as statistically significant. Hazard ratios will be presented with 95% confidence intervals. The analysis will be performed in SPSS.

3. Handling of protocol violations

Wrongly included patients (n=2)

One patient was wrongly included, lacking a Norwegian personal identification number. This identification number is essential to collect information on hospital admissions and death respectively from The Norwegian Patient Registry and The Norwegian Cause of Death Registry. We have therefore chosen to exclude this patient from the analyses.

One patient was wrongly included, in terms of being included in the study earlier, hence the second inclusion actually was a hospital readmission. The second inclusion of the patient is therefore excluded from the analyses.

Patients lost before randomization (n=24)

A few patients were lost before the randomization took place, due to different reasons listed in Figure 1. These 24 patients are will be excluded from all analyses.

Randomized patients who died during the index hospital stay (n=11)

Five patients in the intervention group and six patients in the control group died during the index hospital stay. As we defined the start point for the 12 months follow up at hospital discharge, we have chosen to exclude these 11 patients both from the MITT and PP analysis populations.

Patients not handled according to randomisation

These patients are described under the section *Definition of analysis populations.*

4. Handling of missing data

No missing data on readmissions or mortality is present for the patient population MITT or PP. When data is missing in background variables, results will be presented with specified total number of patients contributing to each variable.

5. Sensitivity analysis

A per protocol analyses will be performed.

6. Variables of adjustments

Since the present study is a randomized controlled trial, there should by default not be done any adjustments. However, if the patients in the control and intervention group turn out to be substantially different in some of the background variables, it will be considered if adjustments have to be made, in additional analyses.

7. Secondary endpoint analysis

Time to the first unplanned hospital readmission within 12 months after index discharge date, censored for deaths, will be analysed with the Kaplan Meier method and the log-rank-test. Hazard ratios with 95% confidence intervals will be estimated using a Cox proportional hazards model.

Total mortality will be analysed as a time-to-event analysis. To exploit the long time period of both inclusion and follow up in the study, all patients will be followed until 31.12.2017 regarding total mortality. The Kaplan Meier method and the log-rank test will be applied. Further, a Cox proportional hazards model will be applied to estimate hazard ratios. Hazard ratios will be presented with 95% confidence intervals.

Continuous variables will be analysed by two-sample t-tests. If extreme outliers are identified, variables will be analysed with the Mann-Whitney test. Proportions will be analysed with the Chi square test.

All analyses will be performed in SPSS. P values below 0.05 will be regarded as statistically significant.

8. Blind analysis

The project administrator and PhD student (ML) has been one of the main study pharmacists, as well as building the research database, has in depth knowledge of the data files, and may recognize whether the patient is in the control or intervention group. Neither the main supervisor (LM) nor the statistician (ES) have been involved in data collection, data punching or in preparation of the data files to statistical analyses.

To maintain blind analyses and prevent bias due to the expectations of the project administrator, data analyses on the primary endpoint, will be performed as follows: ML prepares the data files replacing a random letter to patients in the control group and another random letter to the patients in the intervention group. This new allocation code is written and stored safely and not provided to LM or ES. LM and ES receive the dataset with the new code for the allocated group and carry out the primary analysis. When the statistical analysis is finalized, group allocation will be unblinded by ML, with LM and ES present.

9. References

1. World Health Organization (WHO) Collaboration Centre for Drug Statistics Methodology, ATC/DDD Index. [cited 2018 03.04]. Available from: https://www.whocc.no/atc_ddd_index/.
2. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45(10):1045-51.
3. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
4. Scullin C, Scott MG, Hogg A, McElnay JC. An innovative approach to integrated medicines management. J Eval Clin Pract. 2007;13(5):781-8.

10. Signatures

We hereby vouch for the fidelity of the study to this statistical analysis plan.

Oslo and Trondheim, Norway, 25 th May 2018

Marianne Lea, MSc, PhD student
Project administrator
Hospital Pharmacies Enterprise, South Eastern Norway & University of Oslo

Eva Skovlund, MSc, PhD
Professor of medical statistics
Norwegian University of Science and Technology, NTNU

Liv Mathiesen, MSc, PhD
Associate professor in clinical pharmacy
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Statistical analysis plan amendment 30th May 2018

We discovered that one of the secondary endpoints not was in accordance with a change we made 2th May 2018 after discussions with and recommendations from the Norwegian patients registry (NPR). The following secondary endpoint will therefore be changed from:

- Number of unplanned and planned readmissions per patients within 30 days, 6 months and 12 months after index discharge

to:

- Number of unplanned readmissions per patient within 12 months after index discharge

Documentation:

Excerpt of email correspondence with NPR 2th May 2018:

Fra: Marianne Lea [mailto:mlea10@hotmail.com]
Sendt: 2. mai 2018 08:50
Til: Trude Solbakken
Emne: Re: SV: SV: SV: 17/20673 Søknad om data fra NPR

Hei,

Bra!

Ja, har forstått at dere ikke har data på legevakt/KADer, men at dere hadde info på om sykehusinnleggelsen var akutt eller planlagt? I forhold til reinnleggelser er det akutte innleggelser vi er ute etter, ikke planlagte/elektive.

Hilsen Marianne

2. mai 2018 kl. 08:41 skrev Trude Solbakken <Trude.Solbakken@helsedir.no>:

Excerpt of letter from (original correspondence 13.12.2017)

Avdeling helseregistre skal motta utvalget fra søker. I forbindelse med gjennomgang av søknaden og dialog med søker (08.12.2017 og 12.12.2017) tas det sikte på at det skal utleveres opplysninger om følgende forhold:

- Tidspunkter for innleggelser og utskrivelser for evt siste sykehusopphold de siste 12 mnd før innleggelsedatoen i studien
- Antall sykehusinnleggelser de siste 6 månedene før innleggelsesdatoen i studien
- Tidspunkter for innleggelser og utskrivelser for første gjeninnleggelse på sykehus etter utskrivelsesdatoen i studien
- Antall gjeninnleggelser i løpet av 12 måneder etter utskrivelsesdatoen i studien
- Hovedårsak til første gjeninnleggelse
- Antall kontakter med legevakt i løpet av 12 måneder etter utskrivelsesdatoen i studien

Søker er orientert om at det ikke er mulig å skille mellom legevakt og sykehus, men at det finnes informasjon om kontakten/innleggelsen er ø-hjelp eller planlagt.

TIMELINE OF THE STUDY, MILESTONES

August 15, 2012: Original Trial protocol written

December 20, 2012: Received funding - PhD grant

March 2013 to December 2013: Maternity leave PhD student

January to August 2014 - Practical planning of data inclusion period

May 2014: Necessary approvals obtained

June 2014: Registration of the trial, based on the original trial protocol, in clinicaltrials.gov, identifier: NCT02336113. The trial was published on clinicaltrials.gov`s website in January 2015.*

August 30, 2014: Patient inclusion started

March 17, 2016: Patient inclusion completed

December 31, 2017: Last day of follow-up on readmissions and mortality

June 2017 to May 2018 Application process for outcome data to the Patient Registers**

May 25, 2018: Statistical analysis plan was finalized and signed, hereunder analysis population defined and endpoint analyses detailed

May 29 to June 6, 2018 Outcome data files from Patient registries prepared for analysis

June 8, 2018 Blinded outcome analyses conducted

* Due to a minor Protocol Registration and Results System (PRS) review comment. However, a clarification in the outcome measure, i.e. that readmission data should be collected from the Norwegian Patient Registry, was the only addition made from the original registration made in June 2014.

**Huge workload at the Registers entails a very long processing time for outcome data.