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TITLE PAGE

TITLE

Effect of medicines management versus standard care on readmissions in multimorbid patients: A randomized controlled trial

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ABSTRACT

Objective: To investigate the effect of pharmacist-led medicines management in multimorbid, hospitalized patients on long-term hospital readmissions and survival.

Design: Parallel-group, randomized controlled trial.

Setting: Recruitment from an internal medicine hospital ward in Oslo, Norway. Patients were enrolled consecutively from August 2014 until the predetermined target number of 400 patients. The last participant was enrolled March 2016. Follow-up until December 31, 2017, i.e. 21-40 months.

Participants: Acutely admitted multimorbid patients ≥ 18 years, using minimum four regular drugs from minimum two therapeutic classes. 399 patients were randomly assigned, 1:1, to the intervention or control group. After excluding 11 patients dying in-hospital and 2 erroneously included, the primary analysis comprised 386 patients (193 in each group) with median age 79 years (range 23-96) and number of diseases 7 (range 2-17).

Intervention: Intervention patients received pharmacist-led medicines management comprising medicines reconciliation at admission, repeated medicines reviews throughout the stay and medicines reconciliation and tailored information at discharge, according to the Integrated Medicines Management (IMM) model. Control patients received standard care.

Primary and secondary outcome measures: The primary endpoint was difference in time to readmission or death within 12 months. Overall survival was a priori the clinically most important secondary endpoint.

Results: The pharmacist-led medicines management had no significant effect on time to readmission or death within 12 months after discharge (median 116 versus 184 days, HR

0.82, 95% CI 0.64 to 1.04, p=0.106). A statistically significantly increased overall survival was observed (HR 0.66, 95% CI 0.48 to 0.90, p=0.008).

Conclusions: Pharmacist-led medicines management to multimorbid patients had no statistically significant effect on time until readmission or death. A statistically significant increased overall survival was seen. Further studies should be conducted to investigate the effect of such an intervention on a larger scale.

Trial Registration: ClinicalTrials.gov-Identifier:NCT02336113. The trial is closed for new participants.

ARTICLE SUMMARY

Strengths and limitations of this study

- Randomized controlled design, blinded on the steps possible to blind
- Included almost 200 high-risk multimorbid patients in each group and followed them for 20-41 months
- Hard endpoints, readmissions and mortality, collected from national registers
- Inclusion from a single hospital in Norway
- Spill-over effect may have reduced the effect estimate

KEYWORDS: multimorbid patients, integrated medicines management, pharmacist-led, internal medicine, hospital readmissions, survival

INTRODUCTION

Increased life expectancy and steadily improving healthcare contribute to a growing subpopulation of multimorbid patients, commonly defined as having minimum two conditions.[1-3] The prevalence of multimorbidity is reported to be 20-30% in the general population, 55-98% in the elderly and 22-65% in hospitalized patients.[4-6] Multimorbidity is associated with the use of multiple drugs, increased use of healthcare services and reduced life expectancy.[3, 7-9] The organization of healthcare services and treatment guidelines is however mainly focused on single diagnoses, while coexisting diagnoses or use of multiple drugs are rarely taken into account.[10, 11] Studying the care of multimorbid patients is crucial to managing the future global challenge of ensuring safe, effective and evidence-based care to these patients.[1, 11, 12]

Multimorbid patients using numerous drugs are at high risk of harm by drug-related problems (DRPs).[13, 14] DRPs are reported to cause 10-30% of all hospital admissions, whereof a high proportion is preventable.[15-17] Drugs also cause problems during the hospital stay[18, 19], which pose a risk of readmissions.[20, 21] A recent Cochrane review found no evidence that medicines reviews reduce hospital readmissions or mortality.[22] The authors state that important effects may have been overlooked due to short follow-up in included studies, and request high-quality studies with long follow-up in high-risk patient populations.[22]

The Integrated Medicines Management (IMM) model has been established as a tool for clinical pharmacists to optimize and individualize drug therapy.[23] IMM comprises a systematic approach to ensure high quality of the use of drugs throughout the hospital stay, comprising a three-step procedure, i.e. medicines reconciliation at admission, medicines

reviews during the stay and medicines reconciliation and -information at discharge.[23-27] Nevertheless, only a very limited number of clinical pharmacists are working in Norwegian hospitals, hence standard care for hospitalized patients does not include IMM or other services by clinical pharmacists. Several studies have investigated the effect of implementing either parts of, or the complete IMM model on different efficacy measures[23-25, 28], but to our knowledge, not in multimorbid patients. The objective of the present study was to investigate the effect of pharmacist-led medicines management in multimorbid, hospitalized patients on long-term hospital readmissions and survival.

MATERIALS AND METHODS

Study Design

This parallel-group, randomized controlled trial, approved by the Regional Committee for Medical and Health Research Ethics (2014/704/REK south-eastern D) and the Privacy Ombudsman, was conducted at the internal medicine ward, Oslo University hospital (Ullevaal), Norway. The ward comprised 24 beds and mainly received patients with multiple medical issues, in particular hematological, endocrine, infectious and/or cardiovascular. Patients were considered for inclusion Monday to Friday during regular daytime working hours, from August 30, 2014, until the predetermined target number of 400 patients was enrolled. Eligible patients were prospectively invited and enrolled in the study following written informed consent. S1 Appendix shows the original trial protocol, protocol amendments, the statistical analysis plan and the timeline of the study with the milestones. Figure 1 gives a graphical depiction of the study design, as suggested for studies of complex interventions.[29]

The trial was registered in ClinicalTrials.gov, identifier: NCT02336113, in June 2014. Due to a minor Protocol Registration and Results System (PRS) review comment, the trial was first published on their website in January 2015. A clarification that readmission data were to be harvested from the Norwegian Patient Registry, was the only addition to the original registration. The trial is closed for new participants.

Participants

Inclusion criteria were: acute admission, age ≥ 18 years and use of at least four regular drugs from minimum two therapy classes (Anatomical Therapeutic Chemical (ATC)[30] at 1st level) at admission. The latter was chosen as the preferred multimorbidity measure[31], as drug counts were considered more reliable than disease counts in the acute hospital admission setting. Exclusion criteria were i) terminally ill, ii) isolated due to severe infections or iii) unable to communicate in Norwegian or English and no translator available. Patients readmitted during the study period were not invited for 'a second' inclusion.

Randomization and blinding

The patients were randomized 1:1 to the intervention or control group. Centre for Biostatistics and Epidemiology, Oslo University Hospital, was responsible for the randomization procedure. Their staff had no contact with patients, study pharmacists or ward staff. A random number generator program and a permuted block design were used to generate the randomization sequence, which was delivered to the study pharmacists in sequentially numbered, opaque, sealed envelopes. The investigators were blinded to block size, which was randomly varied. Randomization took place following patient inclusion and baseline assessments. A study pharmacist assigned the envelope with the lowest number to the individual participant and signed the allocation before the envelope was opened.

It was neither feasible to blind participants nor study pharmacists to the allocation. It was also known by ward staff which patients belonged to the intervention group. Ward staff was, however, unable to distinguish between patients randomized to the control group and patients not participating in the trial. The primary endpoint analysis was conducted on a blinded dataset (by researchers who did not see patients). The staff providing outcome data were not involved in data collection or preparation of data files and were blinded to group allocation.

Data collection and baseline assessments

During the inclusion period, six clinical pharmacists, all with a master`s degree in clinical pharmacy and standardized training in IMM, collected data, conducted baseline assessments and provided the various steps of the intervention. All steps were standardized using translated IMM procedures adapted to the Norwegian hospital setting.[23-27, 32] A DRP was defined according to the Pharmaceutical Care Network Europe (PCNE) as "*an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"*.[33]

Blood samples were collected for biochemical analyses. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula[34], except for obese patients (body-mass index > 30), for whom the Salazar-Corcoran formula was used.[35] An experienced senior physician retrospectively collected information from medical records to calculate the Charlson Comorbidity Index (CCI) score.[36]

Before allocation, baseline assessments were conducted for all included patients, comprising medicines reconciliation and review. These medicines reviews included only drugs used prior to admission, not drugs initiated during transport, or following hospital admission. The

pharmacists had access to the patient's medical history and laboratory results up to and including admission time. All medicines discrepancies, i.e. mismatches between the reconciled drug list and the list recorded at hospital admission, and DRPs revealed were registered in the research database, however not systematically discussed in the multidisciplinary treatment team. Before allocation, the study pharmacist assessed whether any medicines discrepancy or DRP could result in irreversible detrimental effects or death if not handled immediately. If the patient was allocated to the control group, any such issue was discussed with a senior physician (MM) who decided whether it was necessary to intervene.

The intervention group – in-hospital pharmacist-led medicines management

The thorough intervention implied the inclusion of clinical pharmacist(s) in the patients` multidisciplinary treatment team throughout the hospital stay, working in close collaboration with the patient, physicians and other members of the team, as shown in Figure 1. The medicines management process can be divided into three parts covering the patients` hospital stay; medicines reconciliation at admission, medicines review repeatedly during the entire stay and medicines reconciliation and tailored information at discharge.[23-27] Medicines reviews were performed at admission and repeatedly as needed due to changes in either prescription, patient symptoms, clinical state, and/or laboratory values. Patients were reviewed for such changes daily, Monday to Friday, during regular daytime working hours.

During medicines reviews, a list of pre-defined risk categories, all described in detail in Table 1, were systematically addressed for each drug in each patient. Furthermore, an overall benefit-risk assessment was made with the main goal of tailoring drug therapy to the

individual participant, giving significant weight to the patient perspective. Medicines discrepancies and DRPs revealed during both baseline assessments and the hospital stay were were discussed in the multidisciplinary treatment team. At discharge, a medicines reconciliation was conducted, followed by written and oral information tailored to the patient's further needs of care, provided to the patient and/or next care provider, see Figure 1. The main goals of this step were to answer drug questions, to ensure continuous treatment, to increase adherence, and to provide the patient and/or next care provider a complete overview of all drugs.

Table 1. Detailed description of the risk categories that were systematically addressed for each drug in each patient during the medicines reviews, and examples of sources used by clinical pharmacists to address them.

Risk category	Detailed description	Examples of sources
Drug monitoring	Need for therapeutic drug monitoring or laboratory monitoring, e.g. digoxin, warfarin, antiepileptics	• The Pharmacology Portal – Norwegian portal for drug and intoxicant analyses - http://www.farmakologiportalen.no/ • Norwegian National Centre for Epilepsy • Centre for Psychopharmacology, Diakonhjemmet Hospital, Norway
Adverse effect	Presence of symptoms or changes in laboratory values possibly caused by drug(s)	• Summary of Product Characteristics (SPC) • UpToDate • Micromedex • CredibleMeds, QTDrugs List, - https://crediblemeds.org/
Drug-drug interaction	Clinically relevant drug-drug interactions	• The Norwegian Medicines Agency – Drug interactions checker • Micromedex – Drug interactions • Drugs.com – Drug interactions checker
Non-optimal drug therapy	Lack of drug treatment or non-optimal drug treatment of a symptom/disease	• Therapy guidelines • BMJ Best Practice • UpToDate • Summary of Product Characteristics (SPC)
Reduced organ function / contraindication	Drug or dosage of drug inappropriate due to reduced kidney function, reduced liver function, contraindications or other diseases.	• The Renal Drug Handbook - https://renaldrugdatabase.com/ • UpToDate • Micromedex • Internetmedicin https://www.internetmedicin.se/searchresult.aspx?search=lever (reduced liver function/drugs that can harm the liver) • Summary of Product Characteristics (SPC)
Inappropriate drug in elderly	Use of less favourable drug in patients >65 years old, e.g. anticholinergics	• STOPP 2 (Screening Tool of Older Persons' Prescriptions) • Beers criteria
Unnecessary drug	Drug in use is not indicated	• Therapy guidelines • Summary of Product Characteristics (SPC) • UpToDate
Course length	Consideration of appropriate duration of course length, e.g. duration of antibiotics	• Summary of Product Characteristics (SPC) • The Norwegian Directorate of Health – National guideline for the use of antibiotics in hospitals • The European Committee on Antimicrobial Susceptibility Testing - EUCAST - minimum inhibitory concentrations
Practical problem	Practical challenges in drug handling, e.g. inhalation devices	• Summary of Product Characteristics (SPC) • Local procedure for tablets and capsules - dividing, opening and crushing • Handbook of Drug Administration via Enteral Feeding Tubes - https://about.medicinescomplete.com/publication/drug-administration-via-enteral-feeding-tubes/
Adherence issue	Patient does not, intentionally or unintentionally, use / take drug as agreed	• Quick guide inhalators - https://sykehusapoteket.no/Documents/Inhalasjonsmedisin%20for%20sykehusleger.pdf • Videos – use of inhalators - https://www.felleskatalogen.no/medisin/bruk-av-inhalatorer/aerochamber
Other	E.g. prescription errors, documentation errors	• The patient`s medical record

The control group - standard care

The control group received standard care, see Figure 1, which in line with standard procedures in Norwegian hospitals did not include either IMM or any other service from clinical pharmacists.

Endpoints

The primary endpoint was time to first hospital readmission or death within 12 months after discharge.

Secondary endpoints:

- Overall survival
- Number of unplanned hospitalizations per patient within 12 months after discharge
- Proportion of patients:
    - with unplanned hospitalizations within 30 days, 6 months and 12 months after discharge
    - who died within 30 days, 6 months, 12 months and 20 months after discharge
    - who died or had unplanned hospitalizations within 30 days, 6 months and 12 months after discharge
- Length of stay (LOS) of first hospital readmission
- Time to the first unplanned readmission within 12 months after discharge, censored for deaths

In the original trial protocol, included in S1 Appendix, *difference between the control and intervention group in time to the first readmission* was defined as the primary endpoint

without further specification. As death is a competing risk to readmissions, it was considered appropriate to use *difference in time to readmission or death* as the primary endpoint. This was clarified in the statistical analysis plan, which was finalized and signed before outcome data files were available.

Data on readmissions were provided by The Norwegian Patient Registry, and data on mortality by The Norwegian Cause of Death Registry. We had originally planned a follow-up of 12 months. However, as both the inclusion period and the retrieval of outcome data took longer than planned, we decided to extend the follow-up of all patients to December 31, 2017 to increase statistical power. This amendment was described in the statistical analysis plan, which was finalized and signed before any outcome data files were available. Beacuse the inclusion period lasted approximately 1.5 year, the follow up of each individual patient was in the range 21 – 40 months.

The primary efficacy analysis excluded patients who died during the index hospital stay as they were never at risk for readmission, as well as erroneously included patients. The analysis population was defined before outcome data files were received.

Sample size

The sample size calculation was based on an expected 12-month readmission frequency of 50%.[23] It was estimated that to detect a 15% absolute reduction in hospital readmissions with 80% power and a significance level of 5%, we would need 168 patients in each group. To compensate for any dropouts, it was decided to enroll 200 patients in each group. Sample size calculations based on proportions are generally considered reliable for survival analysis, but might in some instances over estimate the required sample size.[37] In other words:

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

Statistics

Time-to-event endpoints were compared between groups by the Kaplan Meier method and the log-rank test. Cox's proportional hazards model was applied to estimate hazard ratios (HRs), which are presented with 95% confidence intervals (CIs). The proportionality assumption was checked by visual inspection of log(-log) plots. Continuous variables were compared between the two groups using Mann-Whitney tests.

IBM SPSS Software version 25.0 (IBM Corp. NY), was used for all statistical analyses. P values < 0.05 were regarded as statistically significant.

Patient and Public Involvement

During the planning of the study, patient representatives from the medical clinic participated in the preparation of the patient information leaflet and commented on the study design. Study results will be presented for the patient representatives and they will be involved in choosing the methods and agreeing on plans for dissemination of study results to patients and relevant communities.

RESULTS

During the study period, August 30, 2014, to March 17, 2016, 2174 patients were admitted to the internal medicine ward and 1769 (81%) were assessed for eligibility. Figure 2 shows the patient flow. Among the 598 patients invited to participate, 175 (29%) declined

(permission to register reasons for declining not obtained). 399 patients were randomized, 200 to the intervention group and 199 to the control group. Following randomization, 11 patients (5 intervention and 6 control) who died during the hospital stay and 2 patients (both intervention) who were erroneously included, were excluded from the analyses. Thus, the analysis population for all endpoints comprised 193 patients in each group, all followed-up until December 31, 2017, i.e. for a minimum of 21 months and a maximum 40 months.

The median age in the analysis population was 79 years (range 23-96), 356 (92%) were home-dwelling before hospitalization and 213 (55%) were women. The median number of regular drugs at hospital admission was 8 (range 4-19). The median number of diseases was 7 (range 2-17) and the median CCI score was 3 (range 0-12). The median number of DRPs per patient identified during baseline assessments was 13 (range 3-42). The baseline characteristics of the patients in the control versus the intervention group are presented in Table 2. No differences of importance were observed between the groups.

Table 2. Characteristics of patients in the analysis population.

Characteristic	Control (n=193)	Intervention (n=193)
Women	106 (55%)	102 (53%)
Age	80.7 (23.1-96.4)	78.0 (25.7-95.6)
Number of unplanned hospitalizations last 6 months	1 (0-6)	0 (0-11)
Charlson Comorbidity Index score	3 (0-12)	2 (0-11)
Most frequent medical history:		
• Hypertension	91 (47%)	108 (56%)
• Endocrine and metabolic diseases	77 (40%)	80 (42%)
• Kidney disease	63 (33%)	73 (38%)
• Congestive heart failure	81 (42%)	68 (35%)
• Arythmia	72 (37%)	71 (37%)
Body-mass index[a]	24.4 (14.4-48.4)	25.0 (13.1-43.3)
Laboratory results:		
• Glomerular filtration rate (ml/min)	49 (8-235)	52 (9-229)
• Serum-albumin (g/L)[b]	38 (24-51)	38 (22-56)
• C-reactive protein (nmol/L)	133 (0-3419	152 (0-5248)
Number of prescribed drugs[c] at hospital admission:		
• Regular	8 (4-19)	8 (4-19)
• On demand	2 (0-10)	2 (0-11)
Assistance with drug administration before hospitalization:		
• Multidose	51 (26%)	46 (24%)
• Home nurse	33 (17%)	28 (15%)
• Nursing home	15 (8%)	15 (8%)
• Relative	13 (7%)	14 (7%)
Home-dwelling before hospitalization	178 (92%)	178 (92%)
Number of drug-related problems	13 (3-31)	13 (3-42)
Length of index hospital stay, number of days	8 (2-57)	7 (1-66)
Total number of prescribed drugs at hospital discharge	11 (3-24)	11 (3-23)
Discharged to home	124 (64%)	129 (67%)
Assistance with drug administration after discharge:		
• Multidose	28 (15%)	26 (14%)
• Home nurse	32 (17%)	21 (11%)
• Nursing home	51 (26%)	51 (26%)
• Relative	7 (4%)	11 (6%)
• Other institution/hospital ward	18 (9%)	13 (7%)

Data are n (%) or median (range).

[a] Body-mass index was registered for 144/193 control patients and 148/193 intervention patients.

[b] Serum-albumin was registered for 181/193 control patients and 187/193 intervention patients.

[c] After medicines reconciliation

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In the group receiving pharmacist-led medicines management, a total of 3826 DRPs were revealed at hospital admission and during the hospital stay. Type of DRPs revealed and presented for discussion in the multidisciplinary team and the resepective acceptance rates will be presented in a separate publication. In overall numbers, 1100 of the 3826 identified DRPs (29 %) were solved without the need for discussion in the multidisciplinary treatment team, while 1075 (28%) were not prioritized for discussion, i.e. considered of low importance compared to other DRPs or the patients` clinical state. The remaining 1651 (43 %) DRPs were discussed in the multidisciplinary team, whereof 1022 (62 %) led to immediate changes of the individual patient's drug treatment. In 6 of the 193 control patients (1.5 %) severe medicines discrepancies or DRPs that had to be intervened on were revealed during baseline assessments.

Figure 3a shows time to first readmission or death in the two groups. The median time to readmission or death was 184 days in the intervention group and 116 days in the control group, but the difference was not statistically significant (HR 0.82, 95% CI 0.64 to 1.04, p=0.106). Sensitivity analyses, extending follow-up until December 31, 2017 or excluding control patients who were intervened on, did not influence the effect estimate (HR 0.84, 95% CI 0.68 to 1.05, p=0.118 and HR 0.85, 95% CI 0.68 to 1.06, p=0.149, respectively). The secondary endpoint analysis of time to first readmission, censoring for 20 deaths, gave a similar effect estimate (HR 0.81, 95% CI 0.63-1.04, p=0.104), shown in S2 Figure. There was a statistically significant difference in overall survival (HR 0.66, 95% CI 0.48 to 0.90, p=0.008), as shown in Figure 3b.

The results of other the secondary endpoint analyses are shown in Table 3. Within 20 months after the index discharge, 27% of the intervention patients had died versus 39% of the control patients.

Table 3. Secondary endpoint analyses.

Endpoint	Intervention group (n=193)	Control group (n = 193)
Number of unplanned hospitalizations per patient within 12 months after discharge, median (range)	1 (0-13)	1 (0-12)
Length of hospital stay of first unplanned hospitalization, median number of days (range)	6 (1-58)	6 (1-71)
Number of patients unplanned hospitalized within		
• 30 days after index discharge, n (%)	37 (19)	46 (24)
• 6 months after index discharge, n (%)	89 (46)	103 (53)
• 12 months after index discharge, n (%)	115 (60)	129 (67)
Number of patients who died within		
• 30 days after index discharge, n (%)	4 (2)	7 (4)
• 6 months after index discharge, n (%)	24 (12)	36 (19)
• 12 months after index discharge, n (%)	44 (23)	56 (29)
• 20 months after index discharge, n (%)	52 (27)	76 (39)
Number of patients who died or was unplanned hospitalized within		
• 30 days after index discharge, n (%)	41 (21)	51 (26)
• 6 months after index discharge, n (%)	96 (50)	113 (59)
• 12 months after index discharge, n (%)	125 (65)	139 (72)

DISCUSSION

Pharmacist-led medicines management in multimorbid patients did not statistically significantly prolong the time until first readmission or death compared to control patients. The result are in contrast with previous randomized controlled trials (RCTs) on similar interventions provided to other patient populations, showing a decreased readmission rate, prolonged time to readmission, and a reduction in hospital visits.[23, 38-40] This contrast may be explained by the patient population. To our knowledge, our study is the first to investigate the effect of a medicines management intervention on clinically relevant endpoints in multimorbid patients with complex drug regimens. In this population, urgent

medical care like hospital readmissions, might be difficult to avoid. This theory is supported by a subgroup analysis of one of the previous RCTs, which found that in patients 80 years or older a pharmacist intervention was more effective in preventing emergency department visits in patients using less than 5 drugs compared to patients using 5 drugs or more.[28] However, it should be noted that the 95% confidence interval in our study is wide and compatible with a risk reduction of 36% as well as a 4% increased risk. The sample size calculation in the current study was based on a target 15% reduction in readmissions, which may have been optimistic, and insufficient power may therefore explain the non-significant result.

A statistically significantly increased overall survival, one of the secondary endpoints, was seen in patients in the intervention versus control group. The hazard reduction of 34% is indisputably clinically relevant and reflects a great improvement potential in the care of multimorbid patients. To our knowledge, this is the first study to show an effect of pharmacist-led medicines management on survival. This endpoint was either not investigated[23, 40], or no effect was seen[38, 39] in the previous RCTs. The results of our study are in contrast to the recent Cochrane review concluding that “medication review does not seem to prevent death and hospital readmissions”.[22] The reason for this discrepancy is most likely multifactorial and due to differences in patient populations, characteristics of the interventions, and the duration of the follow-up. Important differences in the patient populations include older patients in the study by Gillespie et al.[38], and that the study by Ravn-Nielsen et al.[41] included patients with lower mortality than the current study, i.e. mortality rates of 10% versus 19%, respectively, in the control group at 6 months after index discharge. In our study, a thorough intervention conducted close to the patient, including medicines reconciliation both at admission and discharge as well as improved

information at discharge to ensure continuous treatment and increase adherence, may constitute characteristics of the intervention important for the effect on survival. Clinical pharmacists performing the procedures of the intervention in close collaboration with the patient, physician and other members of the treatment team are most likely also important for obtaining the effect on survival. At last, the longer follow-up in the present study, prolonged by several months compared to the other RCTs[38, 41], could have allowed prophylactic drugs added during medicine reviews enough time to achieve beneficial effects[22] and probably contributes to explain the intervention`s effect on survival.

Heterogeneity in the pharmacist-led in-hospital interventions, including various elements of various intensity, make comparisons of results amongst studies, as well as interpretation of results, challenging.[22, 42] Furthermore, such interventions are indisputably complex, and evaluating such interventions is complicated.[43, 44] The intervention consists of various components delivered as an overall intervention. With such a design, it is not known whether the overall intervention or only parts of it are important for effect. The intervention in the current study consisted of elements of the highest level of intensity, i.e. diamond level medicines reconciliation[42, 45] and advanced medicines rewiews.[46] In the recent RCT from Denmark, a similar intervention of similar intensity reduced emergency department visits and hospital readmissions, but did not have effect on mortality[41], i.e. the opposite of our results. Differences in eligibility criteria, nuances in the delivered intervention and/or care delivered to control patients, clinical pharmacists` training and how they interacted with the rest of the multidisciplinary treatment team may be factors contributing to explain this. The current study nevertheless adds to the international body of literature that high-intensity, in-hospital pharmacist-led interventions to tailor drug therapy may improve clinical outcomes in high-risk patients.

The intervention had no effect on the length of stay (LOS) of the first readmission. This was not surprising, as hospitals in Norway for several years have received incentives to reduce LOS, illustrated by as short as 6 days median LOS of the first readmission in the present study. In comparison, an IMM-intervention showed a reduction from 13.1 days to 9.7 days LOS of the first readmission in Northern Ireland.[23] The number of unplanned hospitalizations during 12 months follow-up did not differ between the groups in the present study, in line with findings by Gillespie et al.[38]

Drug counts were chosen as the preferred multimorbidity measure at patient inclusion, which could be seen as a limitation. Nonetheless, this strategy resulted in the inclusion of a multimorbid patient population, as validated by diseases counts according to the generally accepted definition.[3] Our study included patients from a single hospital in Norway which may challenge the generalizability. However, the study had few exclusion criteria, thus comprising a broad population. The low drop-out rate further contributes favourably to external validity.

It was not feasible to blind participants, study pharmacists or ward physicians to group allocation. To limit bias, the study was blinded on all steps considered possible to blind. Any spill-over effect of the intervention to control patients would, in any case, reduce the effect estimate. Due to the complexity of the intervention a proportion of the intervention patients did not receive the complete intervention, which may also have contributed to the non-significance on the primary endpoint and an underestimation of the effect on survival. The broad inclusion criteria may have resulted in the inclusion of participants at low risk of readmission and death, which might also have contributed to the non-significant result on the primary endpoint, as well as buffered the effect of the intervention on survival. Studying

the effect of pharmacist-led medicines management in a subgroup of multimorbid patients at the highest risk of readmission, e.g. by stratifying on frailty, could be useful. The randomized controlled design, almost 200 patients in each group, and the long follow-up of all patients are factors that strengthen the study.

CONCLUSION

Pharmacist-led medicines management in-hospital to multimorbid patients had no statistically significant effect on time until readmission or death. A statistically significant increase in overall survival was seen. As a response to the increasing challenges of providing safe and evidence-based healthcare to high-risk multimorbid patients, further studies should be conducted to investigate the effect of such an intervention on a larger scale.

Competing interests statement

Author ML received PhD funding from the South-Eastern Norway Regional Health Authority (grant number 12/00718). The other authors declare that they have no competing interests.

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for positive attitude to the study, and finally Dominic Anthony Hoff for valuable support regarding data punching.

Data sharing statement

The data that support the findings of this study are available from Oslo University Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Deidentified participant data are however available from the authors upon reasonable request and with permission of Oslo University Hospital, with publication. Additional related documents, e.g. patient consent forms, are available at request.

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Disclaimer: Data from the the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

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FIGURE LEGENDS

Figure 1. Title: Graphical depiction of the study design, inspired by Perera and colleagues [29].

Objects are represented by squares and activities by circles.

Figure 2. Title: Patient flow.

Figure 3

a) Title: Time to first hospital readmission or death in the intervention versus control group.

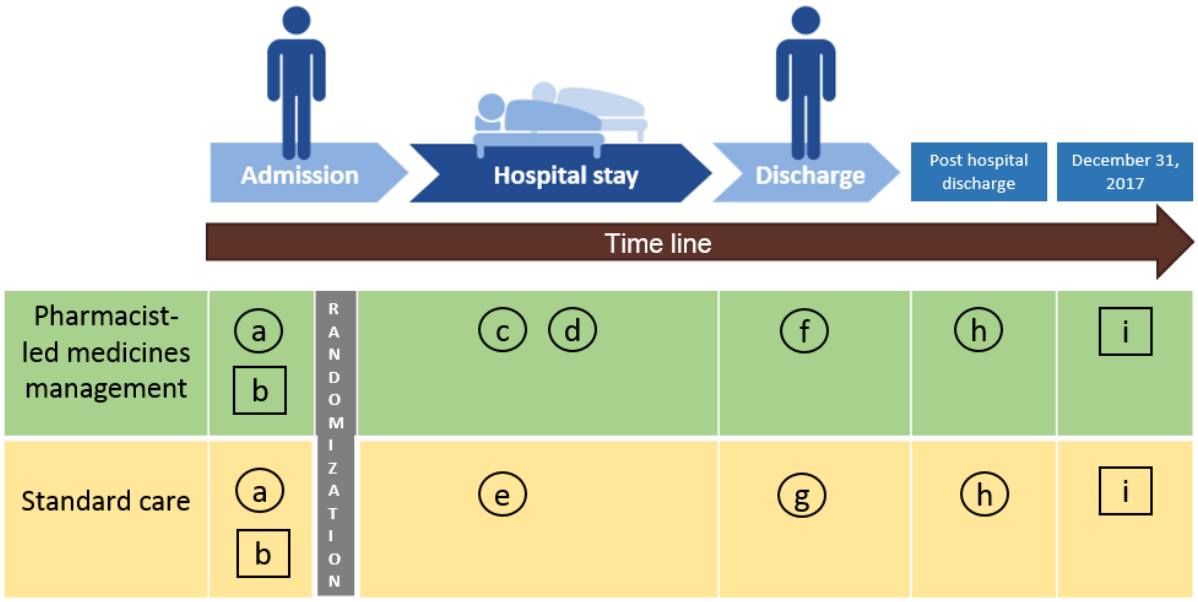
b) Title: Overall survival in the intervention versus control group.

SUPPLEMENTARY MATERIAL

S1 Appendix. Original trial protocol, protocol amendments, statistical analysis plan, statistical analysis plan amendment and timeline of the study with milestones.

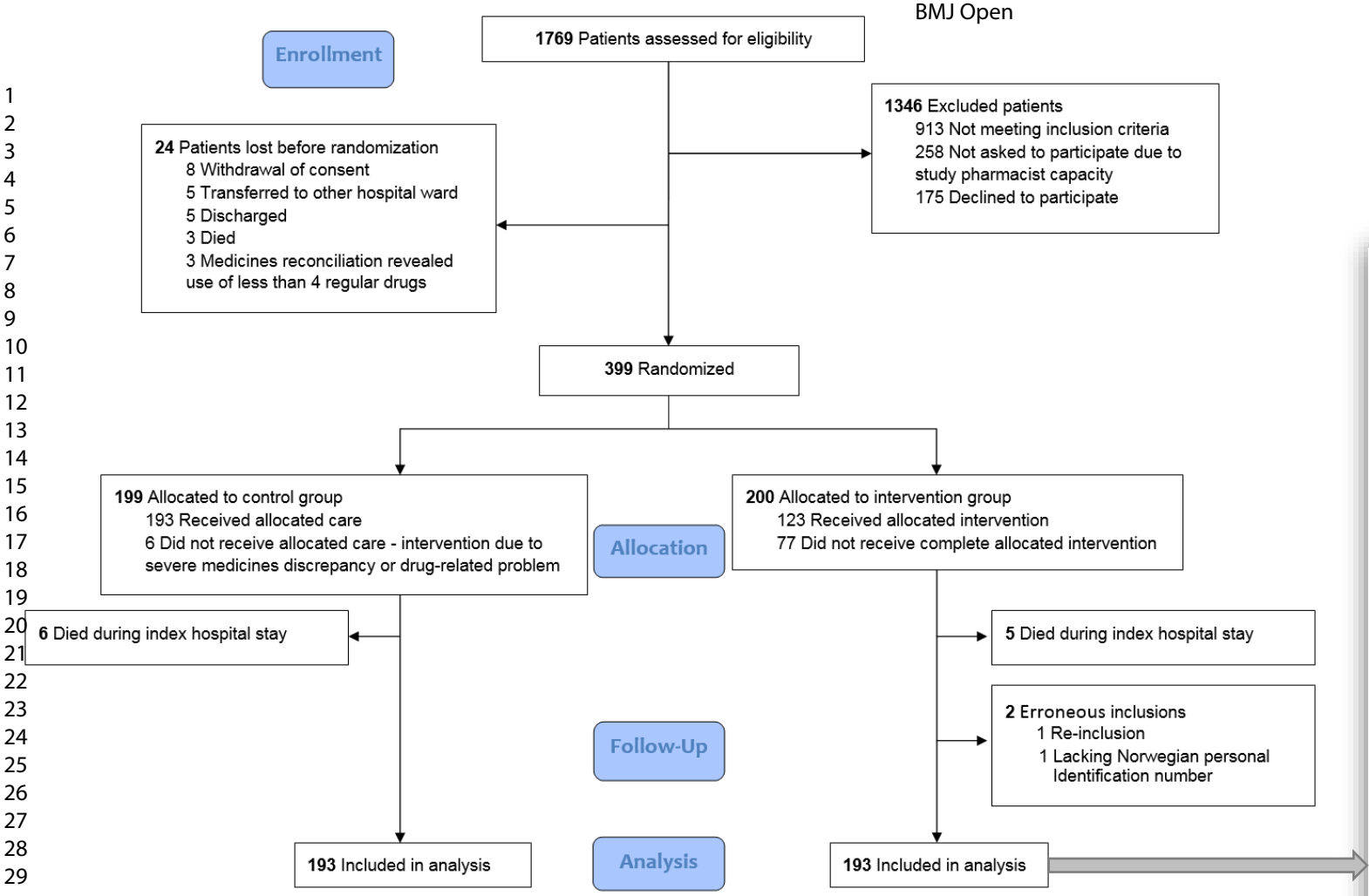
S2 Figure. Time to first hospital readmission in the intervention versus control group, censored for deaths.

S3 Appendix. CONSORT Checklist.



a	Medicines reconciliation and review conducted by clinical pharmacist *without* discussion of medicine discrepancies or drug-related problems (DRPs) and possible solutions in the multidisciplinary team[a]
b	Patient characteristics collected
c	Multidisciplinary treatment team[a] discussions of medicine discrepancies and DRPs revealed at hospital admission and possible solutions
d	Medicines review conducted by clinical pharmacists by systematically addressing 11 pre-defined risk categories for each drug each patient was prescribed at a given point of time; drug monitoring, adverse effect, drug-drug interaction, non-optimal drug therapy, reduced organ function/contraindication, inappropriate drug in elderly, unnecessary drug, course length, practical problem, adherence issue and other. Medicines reviews were performed at admission and repeatedly as needed due to changes in either prescription, patient symptoms, clinical state, and/or laboratory values. Patients were reviewed for such changes daily, Monday to Friday, during regular daytime working hours. Consecutively multidisciplinary treatment team[a] discussions of identified DRPs and possible solutions.
e	Standard in-hospital care provided by physicians with internal medicine expertize, nursing staff and when needed; clinical nutrition physiologists and/or physiotherapists
f	Medicines reconciliation, followed by written and verbal information tailored to the patient`s further needs of care, as well as discharge activities aiming to ensure continuous treatment and increase adherence: • Written systematic information comprising a reconciled drug list with description and justification for all changes made during the hospital stay, to the next care provider[b] (all patients), and to the patient/relative if they to some extent would be involved in handling the drugs after discharge • Verbal information/conversation with the patient and/or relative adapted to the patient needs[c] - if they to some extent would be involved in handling the drugs after discharge • Assistance with retrieving drugs from the pharmacy, if needed • Providing the patient with drugs from the hospital pending on an updated multidose delivery, if needed
g	Discharge medicine information (not standardized) provided by physicians with internal medicine expertize and nursing staff
h	Standard care in the primary health care (details not collected)
i	Last day of follow-up on readmissions and mortality outcomes

[a] The multidisciplinary treatment team consisted of physician with expertise in internal medicine, nursing staff, clinical pharmacist, and when needed; clinical nutrition physiologists and/or physiotherapists
[b] The general practitioner, nursing home, home nurse and/or multidose delivering pharmacy.
[c] Sometimes regarding the entire drug list, sometimes the most important changes, sometimes regarding one specific drug. If the patient was considered to benefit from any provided information or given the opportunity to ask questions, such a targeted conversation was conducted, even if a complex conversation was not considered favorable.



6 No intervention
4 Transferred to other ward
2 Discharged

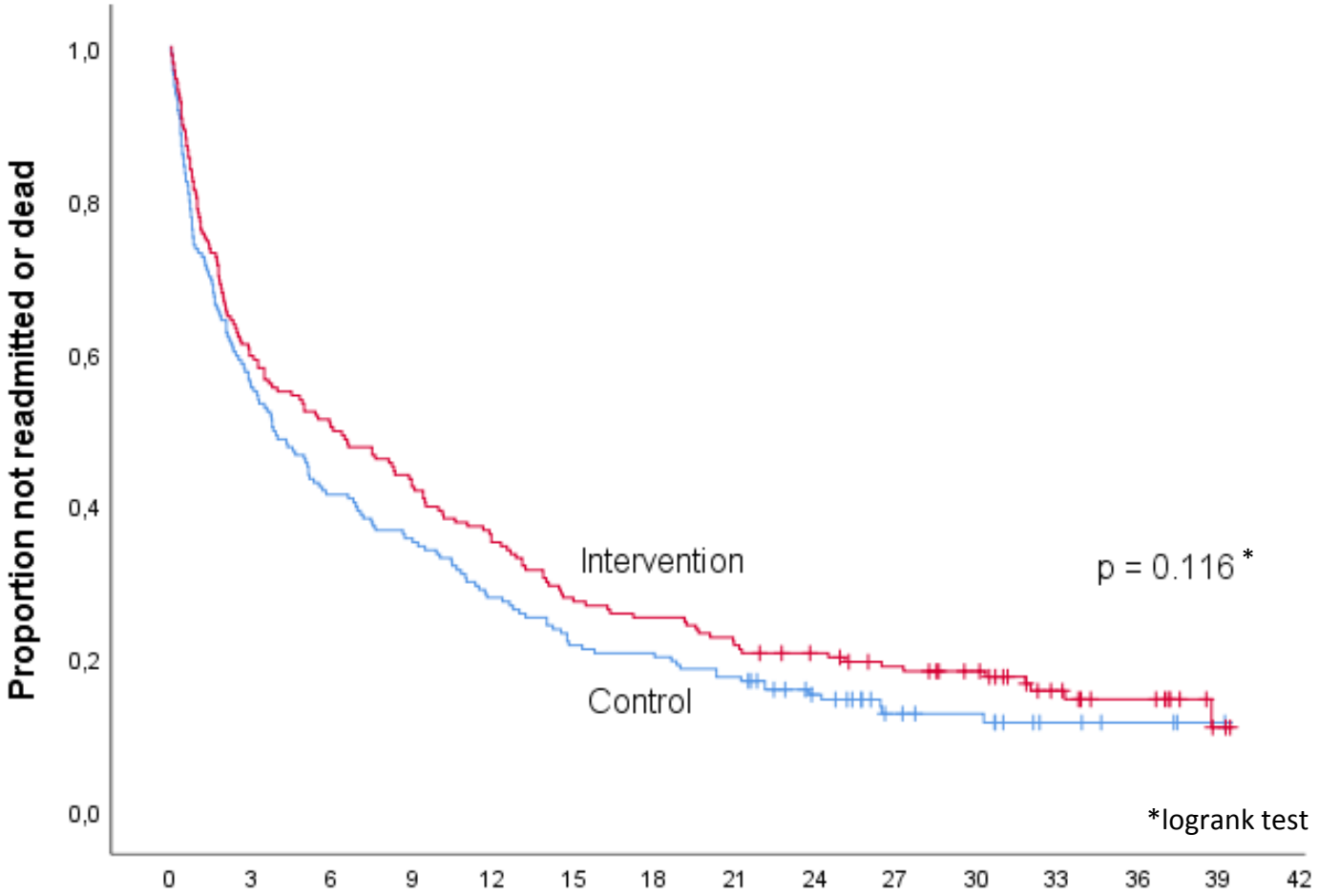
3 Intervention only at hospital admission
1 Then transferred to other ward
2 Then discharged

184 Intervention at hospital admission & during hospital stay

Intervention at hospital discharge

Oral information to patient	Written information to patient	Written information to next care level	Number of patients, n
Not applicable	Not applicable	No	8
No	No	No	14
Yes	No	No	11
No	Yes	No	3
Yes	Yes	No	21
No	Yes	Yes	4
Yes	Yes	Yes	123

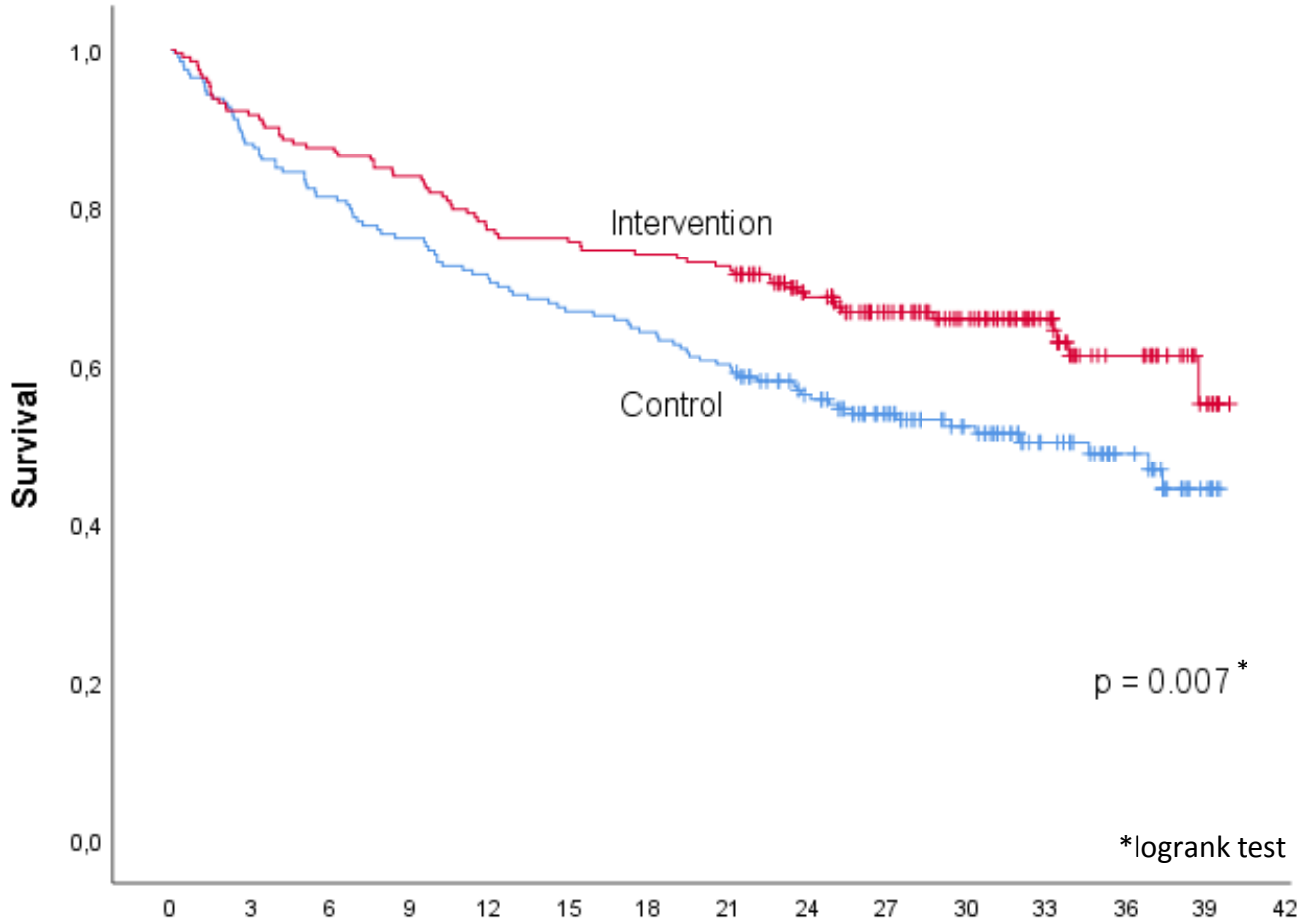
a)



Number at risk

Intervention	193	115	97	82	68	53	49	42	37	31	26	15	10	2
Control	193	107	80	69	54	42	40	34	23	13	11	5	3	1

b)



Number at risk

Intervention	193	177	169	162	149	146	143	140	115	93	73	49	27	8
Control	193	170	157	147	137	129	124	116	97	76	59	40	25	7

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

Project leader and co-supervisor: Associate professor at University of Oslo, Norway, Head of the internal medicine ward at Oslo University Hospital, Norway, MD, PhD Morten Mowe, mormow@ous-hf.no

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- Kristin Thomassen, quality adviser, The Medical Clinic Oslo University Hospital, project member
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- Anette Engnes, master student at the School of Pharmacy, University of Oslo, Norway, project member

Torhild Heggestad, MD, PhD, advisor in Helse-Bergen, Norway, collaborator

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.

Contents

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
xPR	x Patient Registry
REK	Regional ethics committee
UIx	University of x

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

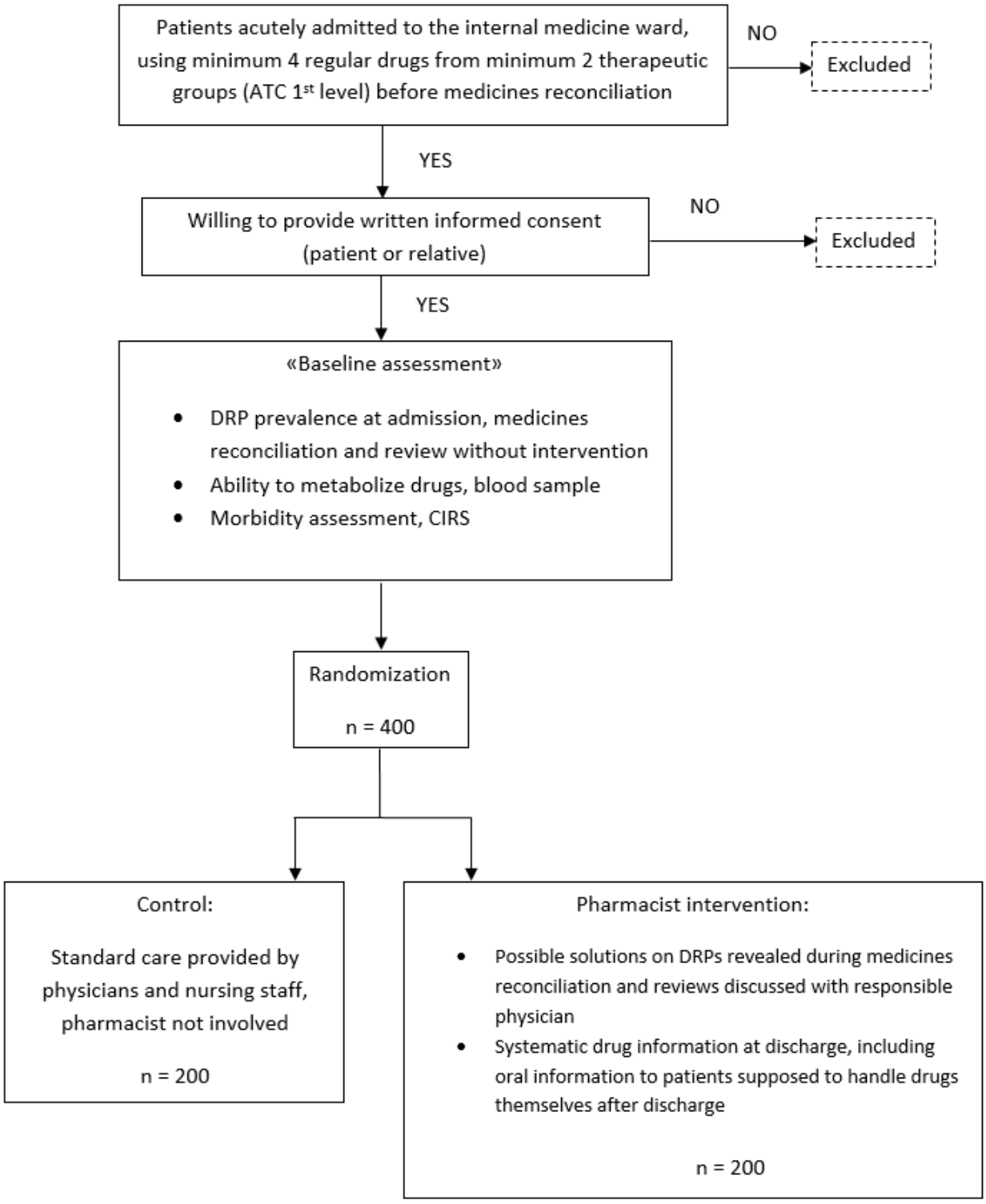

Figure 1. Overview over how the study will be conducted.
ATC = Anatomical Therapeutic Chemical, DRP = drug-related problems, CIRS = Cumulative Illness Rating Scale.

”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.

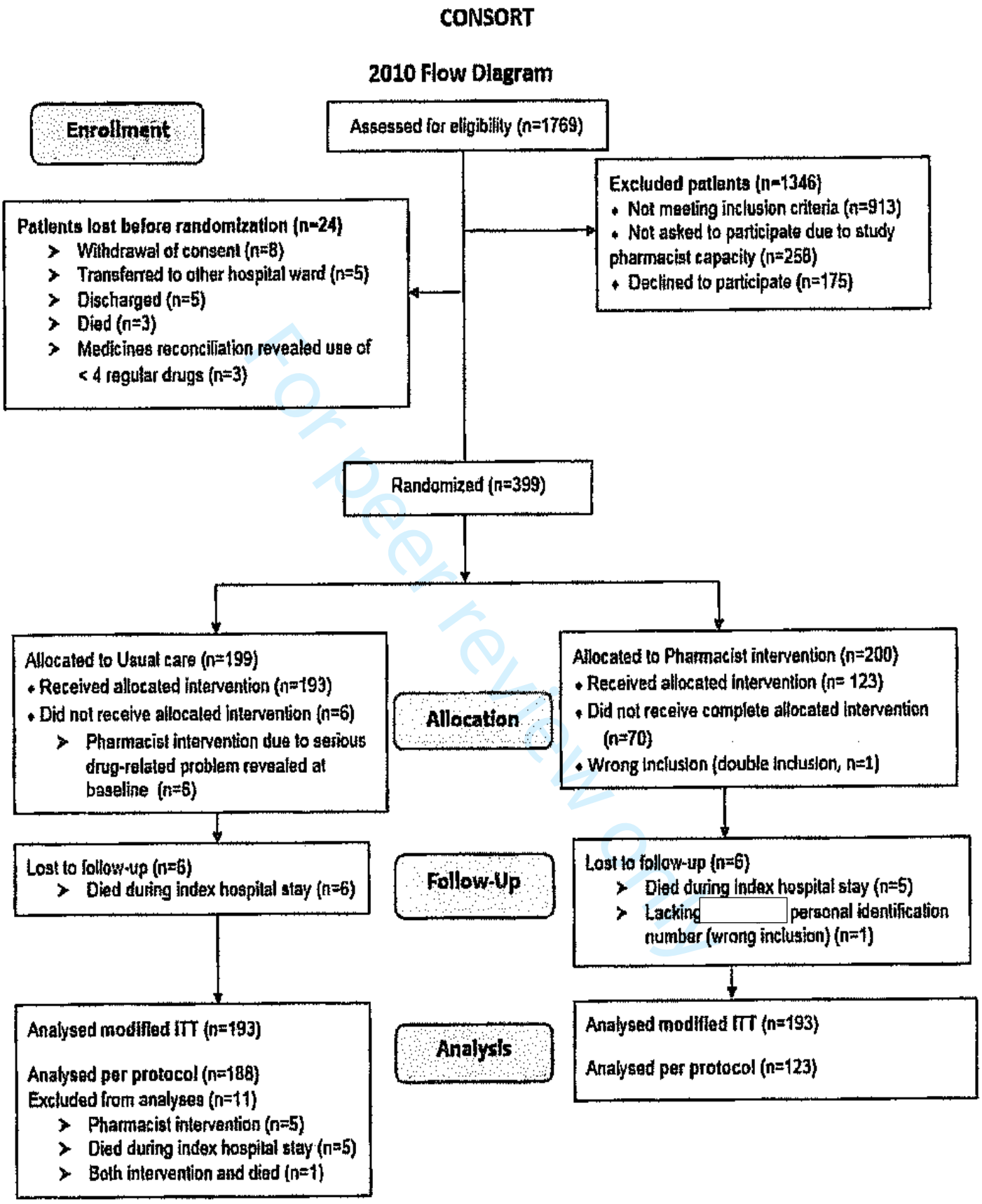
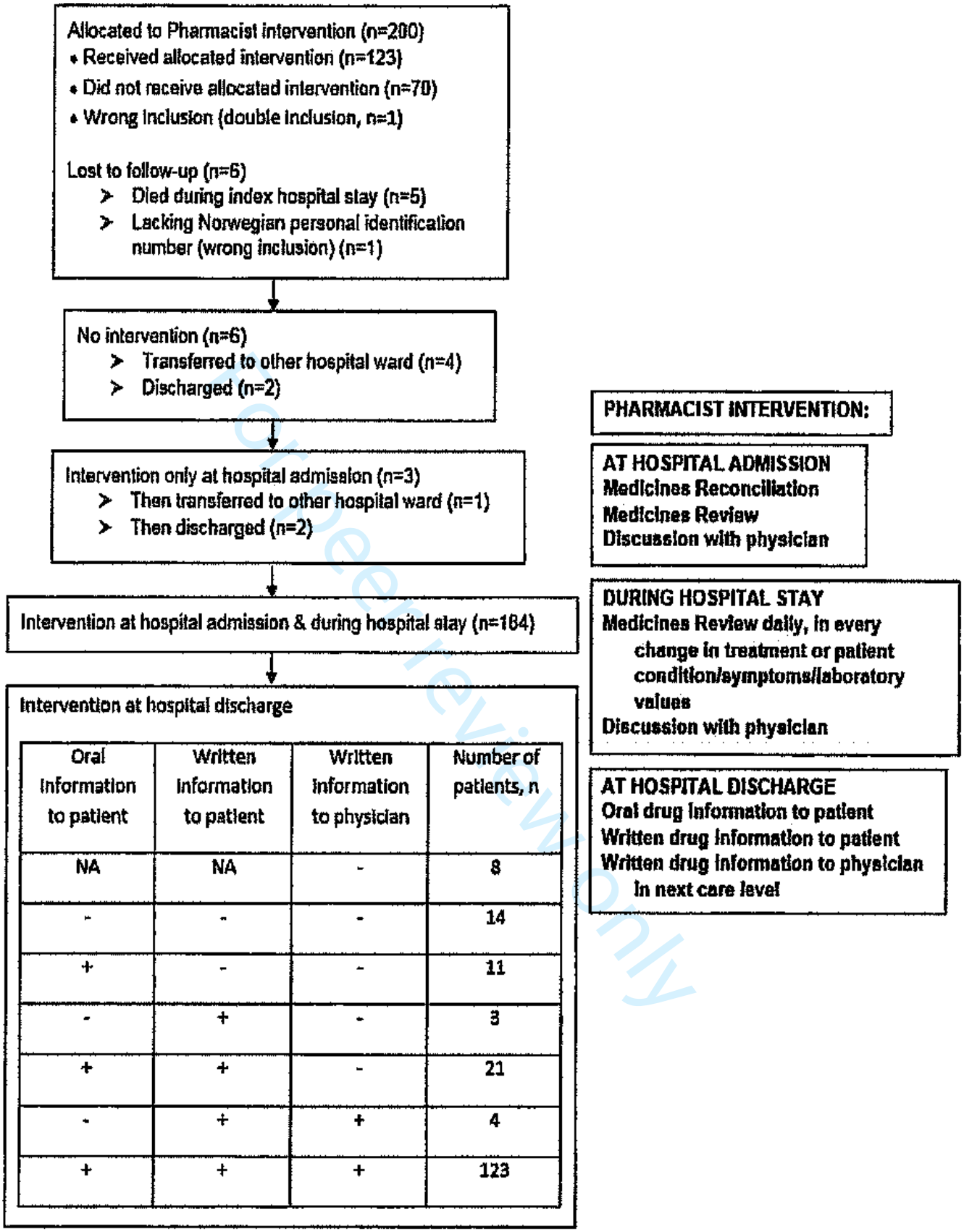


Figure 1. Patient flowchart. ITT = intention to treat.



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

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10. Signatures

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

Oslo and Trondheim, Norway, 25 th May 2018

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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**

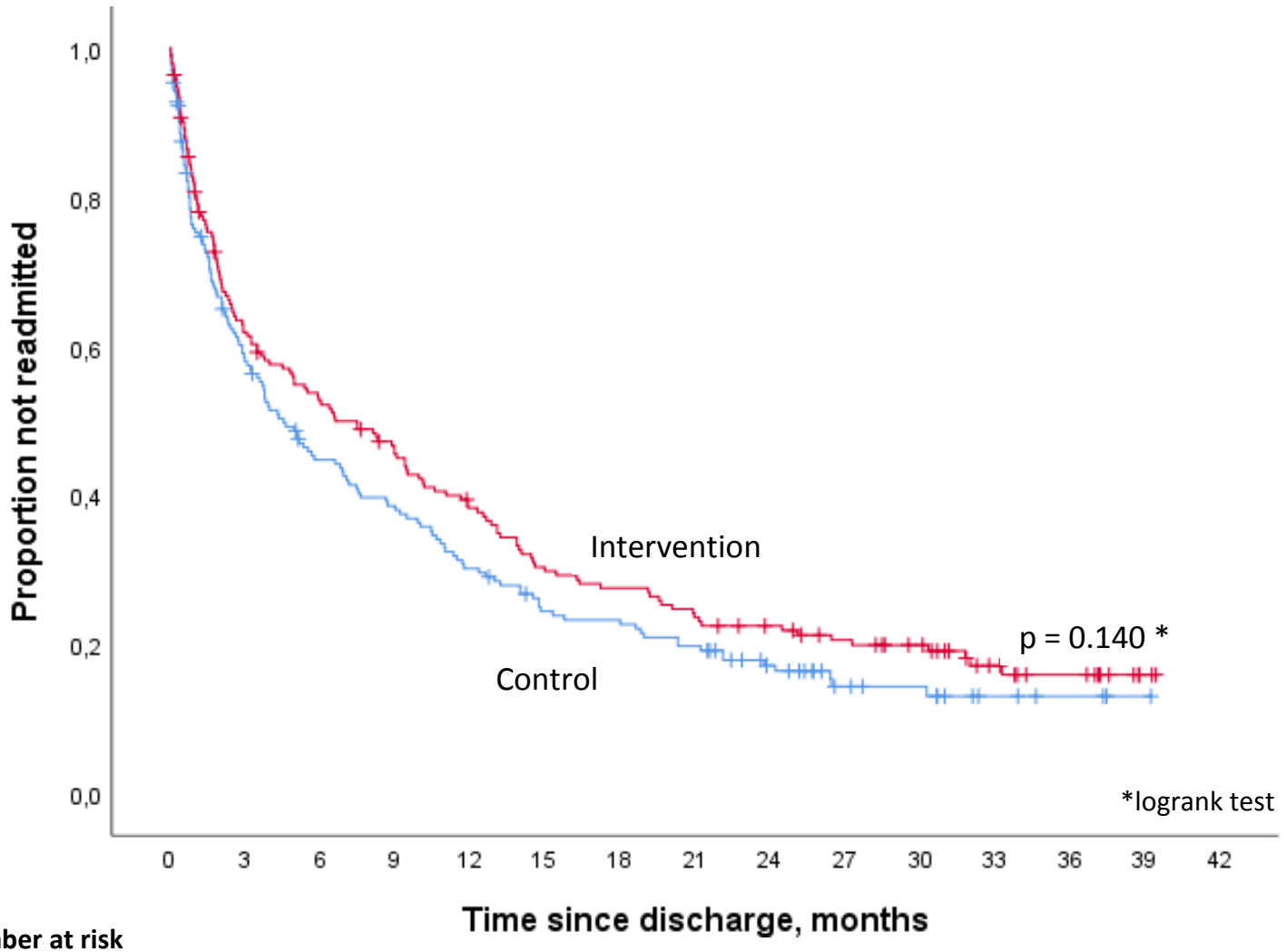
May 25, 2018: Statistical analysis plan was finalized and signed, hereunder analysis population defined and endpoint analyses detailed

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.



Number at risk

Intervention	193	115	97	82	68	53	49	42	37	31	26	15	10	2
Control	193	107	80	69	54	42	40	34	23	13	11	5	3	1

CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial[a]

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.

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Effect of medicines management versus standard care on readmissions in multimorbid patients: A randomized controlled trial

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TITLE PAGE

TITLE

Effect of medicines management versus standard care on readmissions in multimorbid patients: A randomized controlled trial

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ABSTRACT

Objective: To investigate the effect of pharmacist-led medicines management in multimorbid, hospitalized patients on long-term hospital readmissions and survival.

Design: Parallel-group, randomized controlled trial.

Setting: Recruitment from an internal medicine hospital ward in Oslo, Norway. Patients were enrolled consecutively from August 2014 until the predetermined target number of 400 patients. The last participant was enrolled March 2016. Follow-up until December 31, 2017, i.e. 21-40 months.

Participants: Acutely admitted multimorbid patients ≥ 18 years, using minimum four regular drugs from minimum two therapeutic classes. 399 patients were randomly assigned, 1:1, to the intervention or control group. After excluding 11 patients dying in-hospital and 2 erroneously included, the primary analysis comprised 386 patients (193 in each group) with median age 79 years (range 23-96) and number of diseases 7 (range 2-17).

Intervention: Intervention patients received pharmacist-led medicines management comprising medicines reconciliation at admission, repeated medicines reviews throughout the stay and medicines reconciliation and tailored information at discharge, according to the Integrated Medicines Management (IMM) model. Control patients received standard care.

Primary and secondary outcome measures: The primary endpoint was difference in time to readmission or death within 12 months. Overall survival was a priori the clinically most important secondary endpoint.

Results: Pharmacist-led medicines management had no significant effect on the primary endpoint time to readmission or death within 12 months (median 116 versus 184 days, HR

0.82, 95% CI 0.64 to 1.04, p=0.106). A statistically significantly increased overall survival was observed during 21-40 months follow-up (HR 0.66, 95% CI 0.48 to 0.90, p=0.008).

Conclusions: Pharmacist-led medicines management had no statistically significant effect on time until readmission or death. A statistically significant increased overall survival was seen. Further studies should be conducted to investigate the effect of such an intervention on a larger scale.

Trial Registration: ClinicalTrials.gov-Identifier:NCT02336113, closed for new participants.

ARTICLE SUMMARY

Strengths and limitations of this study

- Randomized controlled design, blinded in the steps possible to blind
- Included almost 200 high-risk multimorbid patients in each group and followed them for 20-41 months
- Hard endpoints, readmissions and mortality, collected from national registers
- Inclusion from a single hospital in Norway
- Spill-over effect may have reduced the effect estimate

KEYWORDS: multimorbid patients, integrated medicines management, pharmacist-led, internal medicine, hospital readmissions, survival

INTRODUCTION

Increased life expectancy and steadily improving healthcare contribute to a growing subpopulation of multimorbid patients, commonly defined as having a minimum of two conditions.[1-3] The prevalence of multimorbidity is reported to be 20-30% in the general population, 55-98% in the elderly and 22-65% in hospitalized patients.[4-6] Multimorbidity is associated with the use of multiple drugs, increased use of healthcare services and reduced life expectancy.[3, 7-9] The organization of healthcare services and treatment guidelines is however mainly focused on single diagnoses, while coexisting diagnoses or use of multiple drugs are rarely taken into account.[10, 11] Studying the care of multimorbid patients is crucial to managing the future global challenge of ensuring safe, effective and evidence-based care to these patients.[1, 11, 12]

Multimorbid patients using numerous drugs are at high risk of harm by drug-related problems (DRPs).[13, 14] DRPs are reported to cause 10-30% of all hospital admissions, whereof a high proportion is preventable.[15-17] Drugs also cause problems during the hospital stay[18, 19], which pose a risk of readmissions.[20, 21] A recent Cochrane review found no evidence that medicines reviews reduce hospital readmissions or mortality.[22] The authors state that important effects may have been overlooked due to short follow-up in included studies, and request high-quality studies with long follow-up in high-risk patient populations.[22]

The Integrated Medicines Management (IMM) model has been established as a tool for clinical pharmacists to optimize and individualize drug therapy.[23] IMM comprises a systematic approach to ensure high quality of the use of drugs throughout the hospital stay, comprising a three-step procedure, i.e. medicines reconciliation at admission, medicines

reviews during the stay and medicines reconciliation and -information at discharge.[23-27] Nevertheless, only a very limited number of clinical pharmacists are working in Norwegian hospitals, hence standard care for hospitalized patients does not include IMM or other services by clinical pharmacists. Several studies have investigated the effect of implementing either parts of, or the complete IMM model on different efficacy measures[23-25, 28], but to our knowledge, not in multimorbid patients. The objective of the present study was to investigate the effect of pharmacist-led medicines management in multimorbid, hospitalized patients on long-term hospital readmissions and survival.

MATERIALS AND METHODS

Study Design

This parallel-group, randomized controlled trial, approved by the Regional Committee for Medical and Health Research Ethics (2014/704/REK south-eastern D) and the Privacy Ombudsman, was conducted at the internal medicine ward, Oslo University hospital (Ullevaal), Norway. The ward comprised 24 beds and mainly received patients with multiple medical issues, in particular hematological, endocrine, infectious and/or cardiovascular. Patients were considered for inclusion Monday to Friday during regular daytime working hours, from August 30, 2014, until the predetermined target number of 400 patients was enrolled. Eligible patients were prospectively invited and enrolled in the study following written informed consent. S1 Appendix shows the original trial protocol, protocol amendments, the statistical analysis plan and the timeline of the study with the milestones. S2 Appendix shows the CONSORT Checklist. Figure 1 gives a graphical depiction of the study design, as suggested for studies of complex interventions.[29]

The trial was registered in ClinicalTrials.gov, identifier: NCT02336113, in June 2014. Due to a minor Protocol Registration and Results System (PRS) review comment, the trial was first published on their website in January 2015. A clarification that readmission data were to be harvested from the Norwegian Patient Registry, was the only addition to the original registration. The trial is closed for new participants.

Participants

Inclusion criteria were: acute admission, age ≥ 18 years and use of at least four regular drugs from minimum two therapy classes (Anatomical Therapeutic Chemical (ATC)[30] at 1st level) at admission. The latter was chosen as the preferred multimorbidity measure[31], as drug counts were considered more reliable than disease counts in the acute hospital admission setting. Drugs were counted before medicines reconciliation. However, if the medicines reconciliation revealed that this inclusion criterion was not fulfilled, the patient was excluded from the study. Exclusion criteria were i) terminally ill, ii) isolated due to severe infections or iii) unable to communicate in Norwegian or English and no translator available. Patients readmitted during the study period were not invited for 'a second' inclusion.

Randomization and blinding

The patients were randomized 1:1 to the intervention or control group. Centre for Biostatistics and Epidemiology, Oslo University Hospital, was responsible for the randomization procedure. Their staff had no contact with patients, study pharmacists or ward staff. A random number generator program and a permuted block design were used to generate the randomization sequence, which was delivered to the study pharmacists in sequentially numbered, opaque, sealed envelopes. The investigators were blinded to block size, which was randomly varied. Randomization took place following patient inclusion and

baseline assessments. A study pharmacist assigned the envelope with the lowest number to the individual participant and signed the allocation before the envelope was opened.

It was neither feasible to blind participants nor study pharmacists to the allocation. It was also known by ward staff which of the patients belonged to the intervention group. Ward staff was, however, unable to distinguish between patients randomized to the control group and patients not participating in the trial. The primary endpoint analysis was conducted on a blinded dataset (by researchers who did not see patients). The staff from the Norwegian Patient Registry and the Norwegian Cause of Death Registry providing outcome data were not involved in data collection or preparation of data files and were blinded to group allocation.

Data collection and baseline assessments

During the inclusion period, six clinical pharmacists, all with a master`s degree in clinical pharmacy and standardized training in IMM, collected data, conducted baseline assessments and provided the various steps of the intervention. All steps were standardized using translated IMM procedures adapted to the Norwegian hospital setting.[23-27, 32] A DRP was defined according to the Pharmaceutical Care Network Europe (PCNE) as *"an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"*.[33]

Blood samples were collected for biochemical analyses. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula[34], except for obese patients (body-mass index > 30), for whom the Salazar-Corcoran formula was used.[35] An experienced senior physician retrospectively collected information from medical records to calculate the Charlson Comorbidity Index (CCI) score.[36]

Before allocation, baseline assessments were conducted for all included patients, comprising medicines reconciliation and review. The purpose of these baseline assessments was to assess the prevalence of DRPs and drug-related hospitalizations [37]. These medicines reviews included only drugs used before admission, not drugs initiated during transport, or following hospital admission. The pharmacists had access to the patient's medical history and laboratory results up to and including admission time. Importantly though, medicines discrepancies, i.e. mismatches between the reconciled drug list and the list recorded at hospital admission, and DRPs revealed during these baseline assessments were *not* discussed in the multidisciplinary treatment team. Before allocation, the study pharmacist assessed whether any medicines discrepancy or DRP could result in irreversible detrimental effects or death if not handled immediately. If the patient was allocated to the control group, any such issue was discussed with a senior physician (MM) who decided whether it was necessary to intervene.

The intervention group – in-hospital pharmacist-led medicines management

The thorough intervention implied the inclusion of clinical pharmacist(s) in the patients` multidisciplinary treatment team throughout the hospital stay, working in close collaboration with the patient, physicians and other members of the team, as shown in Figure 1. The medicines management process can be divided into three parts covering the patients` hospital stay; medicines reconciliation at admission, medicines review repeatedly during the entire stay and medicines reconciliation and tailored information at discharge.[23-27] Medicines reviews were performed at admission and repeatedly as needed due to changes in either prescription, patient symptoms, clinical state, and/or

laboratory values. Patients were reviewed for such changes daily, Monday to Friday, during regular daytime working hours.

During medicines reviews, a list of pre-defined risk categories, all described in detail in Table 1, were systematically addressed for each drug in each patient. Furthermore, an overall benefit-risk assessment was made with the main goal of tailoring drug therapy to the individual participant, giving significant weight to the patient perspective. Medicines discrepancies and DRPs revealed during both baseline assessments and the hospital stay were discussed in the multidisciplinary treatment team. At discharge, a medicines reconciliation was conducted, followed by written and oral information tailored to the patient's further needs of care, provided to the patient and/or next care provider, see Figure 1. The main goals of this step were to answer drug questions, to ensure continuous treatment, to increase adherence, and to provide the patient and/or next care provider a complete overview of all drugs.

Table 1. Detailed description of the risk categories that were systematically addressed for each drug in each patient during the medicines reviews, and examples of sources used by clinical pharmacists to address them.

Risk category	Detailed description	Examples of sources
Drug monitoring	Need for therapeutic drug monitoring or laboratory monitoring, e.g. digoxin, warfarin, antiepileptics	• The Pharmacology Portal – Norwegian portal for drug and intoxicant analyses - http://www.farmakologiportalen.no/ • Norwegian National Centre for Epilepsy • Centre for Psychopharmacology, Diakonhjemmet Hospital, Norway
Adverse effect	Presence of symptoms or changes in laboratory values possibly caused by drug(s)	• Summary of Product Characteristics (SPC) • UpToDate • Micromedex • CredibleMeds, QTDrugs List, - https://crediblemeds.org/
Drug-drug interaction	Clinically relevant drug-drug interactions	• The Norwegian Medicines Agency – Drug interactions checker • Micromedex – Drug interactions • Drugs.com – Drug interactions checker
Non-optimal drug therapy	Lack of drug treatment or non-optimal drug treatment of a symptom/disease	• Therapy guidelines • BMJ Best Practice • UpToDate • Summary of Product Characteristics (SPC)
Reduced organ function / contraindication	Drug or dosage of drug inappropriate due to reduced kidney function, reduced liver function, contraindications or other diseases.	• The Renal Drug Handbook - https://renaldrugdatabase.com/ • UpToDate • Micromedex • Internetmedicin https://www.internetmedicin.se/searchresult.aspx?search=lever (reduced liver function/drugs that can harm the liver) • Summary of Product Characteristics (SPC)
Inappropriate drug in elderly	Use of less favourable drug in patients over 65 years old, e.g. anticholinergics	• STOPP 2 (Screening Tool of Older Persons' Prescriptions) • Beers criteria
Unnecessary drug	Drug in use is not indicated	• Therapy guidelines • Summary of Product Characteristics (SPC) • UpToDate
Course length	Consideration of appropriate duration of course length, e.g. duration of antibiotics	• Summary of Product Characteristics (SPC) • The Norwegian Directorate of Health – National guideline for the use of antibiotics in hospitals • The European Committee on Antimicrobial Susceptibility Testing - EUCAST - minimum inhibitory concentrations
Practical problem	Practical challenges in drug handling, e.g. inhalation devices	• Summary of Product Characteristics (SPC) • Local procedure for tablets and capsules - dividing, opening and crushing • Handbook of Drug Administration via Enteral Feeding Tubes - https://about.medicinescomplete.com/publication/drug-administration-via-enteral-feeding-tubes/
Adherence issue	Patient does not, intentionally or unintentionally, use / take drug as agreed	• Quick guide inhalators - https://sykehusapoteket.no/Documents/Inhalasjonsmedisin%20for%20sykehusleger.pdf • Videos – use of inhalators - https://www.felleskatalogen.no/medisin/bruk-av-inhalatorer/aerochamber
Other	Problem not applicable in other subgroups, e.g. prescription errors, documentation errors	• The patient`s medical record

The control group - standard care

The control group received standard care, see Figure 1, which in line with standard procedures in Norwegian hospitals included neither medicines reconciliation nor medicines reviews or any other service from clinical pharmacists. Medicines discrepancies and DRPs revealed during baseline assessments in control patients were only registered in the research database, and not discussed in the multidisciplinary treatment team.

Endpoints

The primary endpoint was time to first hospital readmission or death within 12 months after discharge.

Secondary endpoints:

- Overall survival
- Number of unplanned hospitalizations per patient within 12 months after discharge
- Proportion of patients:
    - with unplanned hospitalizations within 30 days, 6 months and 12 months after discharge
    - who died within 30 days, 6 months, 12 months and 20 months after discharge
    - who died or had unplanned hospitalizations within 30 days, 6 months and 12 months after discharge
- Length of stay (LOS) of first hospital readmission
- Time to the first unplanned readmission within 12 months after discharge, censored for deaths

In the original trial protocol, included in S1 Appendix, the *difference between the control and intervention group in time to the first readmission* was defined as the primary endpoint without further specification. As death is a competing risk to readmissions, it was considered appropriate to use the *difference in time to readmission or death* as the primary endpoint. This was clarified in the statistical analysis plan, which was finalized and signed before outcome data files were available.

Data on readmissions were provided by the Norwegian Patient Registry and data on mortality by the Norwegian Cause of Death Registry. We had originally planned a follow-up of 12 months. However, as both the inclusion period and the retrieval of outcome data took longer than planned, we decided to extend the follow-up of all patients to December 31, 2017, to increase statistical power. This amendment was described in the statistical analysis plan, which was finalized and signed before any outcome data files were available. Because the inclusion period lasted approximately 1.5 years, the follow up of each individual patient was in the range 21 – 40 months.

The primary efficacy analysis was a modified intention to treat-analysis excluding patients who died during the index hospital stay as they were never at risk for readmission, as well as erroneously included patients. The analysis population was defined before outcome data files were received.

Sample size

The sample size calculation was based on an expected 12-month readmission frequency of 50%.[23] It was estimated that to detect a 15% absolute reduction in hospital readmissions with 80% power and a significance level of 5%, we would need 168 patients in each group. To compensate for any dropouts, it was decided to enroll 200 patients in each group. Sample

size calculations based on proportions are generally considered reliable for survival analysis, but might in some instances overestimate the required sample size.[38] In other words: since a survival analysis utilizes the information better than a comparison of proportions at a given time, the power will be somewhat higher than estimated above.

Statistics

Time-to-event endpoints were compared between groups by the Kaplan Meier method and the log-rank test. Cox's proportional hazards model was applied to estimate hazard ratios (HRs), which are presented with 95% confidence intervals (CIs). The proportionality assumption was checked by visual inspection of log(-log) plots. Continuous variables were compared between the two groups using Mann-Whitney tests. In an additional sensitivity analysis of time to readmission, which was not included in the statistical analysis plan, death was treated as a competing risk using the Fine and Gray method [39].

Statistical analyses were performed by IBM SPSS Software version 25.0 (IBM Corp. NY) and STATA 16. P values < 0.05 were regarded as statistically significant.

Patient and Public Involvement

During the planning of the study, patient representatives from the medical clinic participated in the preparation of the patient information leaflet and provided input on the study design, e.g. the choice of the primary endpoint.

RESULTS

During the study period, August 30, 2014, to March 17, 2016, 2174 patients were admitted to the internal medicine ward and 1769 (81%) were assessed for eligibility. Figure 2 shows the patient flow. Among the 598 patients invited to participate, 175 (29%) declined

(permission to register reasons for declining not obtained). 399 patients were randomized, 200 to the intervention group and 199 to the control group. Following randomization, 11 patients (5 intervention and 6 control) who died during the hospital stay and 2 patients (both intervention) who were erroneously included, were excluded from the analyses. Thus, the analysis population for all endpoints comprised 193 patients in each group, all followed-up until December 31, 2017, i.e. for a minimum of 21 months and a maximum of 40 months.

The median age in the analysis population was 79 years (range 23-96), 356 (92%) were home-dwelling before hospitalization and 213 (55%) were women. The median number of regular drugs at hospital admission was 8 (range 4-19). The median number of diseases was 7 (range 2-17) and the median CCI score was 3 (range 0-12). The median number of DRPs per patient identified during baseline assessments was 13 (range 3-42). The baseline characteristics of the patients in the control versus the intervention group are presented in Table 2. No differences of importance were observed between the groups.

Table 2. Characteristics of patients in the analysis population.

Characteristic	**Control (n=193)**	**Intervention (n=193)**
Women	106 (55%)	102 (53%)
Age	80.7 (23.1-96.4)	78.0 (25.7-95.6)
Number of unplanned hospitalizations last 6 months	1 (0-6)	0 (0-11)
Charlson Comorbidity Index score	3 (0-12)	2 (0-11)
Most frequent medical history:		
• Hypertension	91 (47%)	108 (56%)
• Endocrine and metabolic diseases	77 (40%)	80 (42%)
• Kidney disease	63 (33%)	73 (38%)
• Congestive heart failure	81 (42%)	68 (35%)
• Arrhythmia	72 (37%)	71 (37%)
Body-mass index[a]	24.4 (14.4-48.4)	25.0 (13.1-43.3)
Laboratory results:		
• Glomerular filtration rate (ml/min)	49 (8-235)	52 (9-229)
• Serum-albumin (g/L)[b]	38 (24-51)	38 (22-56)
• C-reactive protein (nmol/L)	133 (0-3419	152 (0-5248)
Number of prescribed drugs[c] at hospital admission:		
• Regular	8 (4-19)	8 (4-19)
• On demand	2 (0-10)	2 (0-11)
Assistance with drug administration before hospitalization:		
• Multidose	51 (26%)	46 (24%)
• Home nurse	33 (17%)	28 (15%)
• Nursing home	15 (8%)	15 (8%)
• Relative	13 (7%)	14 (7%)
Home-dwelling before hospitalization	178 (92%)	178 (92%)
Number of drug-related problems	13 (3-31)	13 (3-42)
Length of index hospital stay, number of days	8 (2-57)	7 (1-66)
Total number of prescribed drugs at hospital discharge	11 (3-24)	11 (3-23)
Discharged to home	124 (64%)	129 (67%)
Assistance with drug administration after discharge:		
• Multidose	28 (15%)	26 (14%)
• Home nurse	32 (17%)	21 (11%)
• Nursing home	51 (26%)	51 (26%)
• Relative	7 (4%)	11 (6%)
• Other institution/hospital ward	18 (9%)	13 (7%)

Data are n (%) or median (range).

[a] Body-mass index was registered for 144/193 control patients and 148/193 intervention patients.

[b] Serum-albumin was registered for 181/193 control patients and 187/193 intervention patients.

[c] After medicines reconciliation

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In the group receiving pharmacist-led medicines management, a total of 3826 DRPs were revealed at hospital admission and during the hospital stay. Type of DRPs revealed and presented for discussion in the multidisciplinary team and the respective acceptance rates will be presented in a separate publication. In overall numbers, 1100 of the 3826 identified DRPs (29 %) were solved without the need for discussion in the multidisciplinary treatment team, while 1075 (28%) were not prioritized for discussion, i.e. considered of low importance compared to other DRPs or the patients` clinical state. The remaining 1651 (43 %) DRPs were discussed in the multidisciplinary team, whereof 1022 (62 %) led to immediate changes in the individual patient's drug treatment. In 6 of the 193 control patients (1.5 %) severe medicines discrepancies or DRPs that had to be intervened on were revealed during baseline assessments.

Figure 3a shows time to first readmission or death in the two groups. The median time to readmission or death was 184 days in the intervention group and 116 days in the control group, but the difference was not statistically significant (HR 0.82, 95% CI 0.64 to 1.04, p=0.106). Sensitivity analyses, extending follow-up until December 31, 2017, or excluding control patients who were intervened on, did not influence the effect estimate (HR 0.84, 95% CI 0.68 to 1.05, p=0.118 and HR 0.85, 95% CI 0.68 to 1.06, p=0.149, respectively). The secondary endpoint analysis of time to first readmission, censoring for 20 deaths, gave a similar effect estimate (HR 0.81, 95% CI 0.63-1.04, p=0.104), shown in S3 Appendix. When death was instead treated as a competing risk the subdistribution hazard ratio was SHR 0.83, 95%CI 0.64-1.06, p=0.137.

There was a statistically significant difference in overall survival (HR 0.66, 95% CI 0.48 to 0.90, p=0.008), as shown in Figure 3b. The results of other the secondary endpoint analyses

are shown in Table 3. Within 20 months after the index discharge, 27% of the intervention patients had died versus 39% of the control patients.

Table 3. Secondary endpoint analyses.

Endpoint	Intervention group (n=193)	Control group (n=193)	p value
Number of unplanned hospitalizations per patient within 12 months after discharge, median (range)	1 (0-13)	1 (0-12)	0.212
Length of hospital stay of first unplanned hospitalization, median number of days (range)	6 (1-58)	6 (1-71)	0.576
Number of patients unplanned hospitalized within			
• 30 days after index discharge, n (%)	37 (19)	46 (24)	0.265
• 6 months after index discharge, n (%)	89 (46)	103 (53)	0.154
• 12 months after index discharge, n (%)	115 (60)	129 (67)	0.139
Number of patients who died within			
• 30 days after index discharge, n (%)	4 (2)	7 (4)	0.359
• 6 months after index discharge, n (%)	24 (12)	36 (19)	0.092
• 12 months after index discharge, n (%)	44 (23)	56 (29)	0.163
• 20 months after index discharge, n (%)	52 (27)	76 (39)	0.009
Number of patients who died or was unplanned hospitalized within			
• 30 days after index discharge, n (%)	41 (21)	51 (26)	0.232
• 6 months after index discharge, n (%)	96 (50)	113 (59)	0.082
• 12 months after index discharge, n (%)	125 (65)	139 (72)	0.125

DISCUSSION

Pharmacist-led medicines management in multimorbid patients did not statistically significantly prolong the time until first readmission or death compared to control patients. The result is in contrast with previous randomized controlled trials (RCTs) on similar interventions provided to other patient populations, showing a decreased readmission rate, prolonged time to readmission, and a reduction in hospital visits.[23, 40-42] This contrast may be explained by the patient population. To our knowledge, our study is the first to investigate the effect of a medicines management intervention on clinically relevant endpoints in multimorbid patients with complex drug regimens. In this population, urgent

medical care like hospital readmissions might be difficult to avoid. This theory is supported by a subgroup analysis of one of the previous RCTs, which found that in patients 80 years or older a pharmacist intervention was more effective in preventing emergency department visits in patients using less than 5 drugs compared to patients using 5 drugs or more.[28] However, it should be noted that the 95% confidence interval in our study is wide and compatible with a risk reduction of 36% as well as a 4% increased risk. The sample size calculation in the current study was based on a target 15% reduction in readmissions, which may have been optimistic, and insufficient power may therefore explain the non-significant result.

A statistically significantly increased overall survival, one of the secondary endpoints, was seen in patients in the intervention versus the control group. The hazard reduction of 34% is indisputably clinically relevant and reflects a great improvement potential in the care of multimorbid patients. To our knowledge, this is the first study to show an effect of pharmacist-led medicines management on survival. This endpoint was either not investigated[23, 42], or no effect was seen[40, 41] in the previous RCTs. The results of our study are in contrast to the recent Cochrane review concluding that “medication review does not seem to prevent death and hospital readmissions”.[22] The reason for this discrepancy is most likely multifactorial and due to differences in patient populations, characteristics of the interventions, and the duration of the follow-up. Important differences in the patient populations include older patients in the study by Gillespie et al.[40], and that the study by Ravn-Nielsen et al.[43] included patients with lower mortality than the current study, i.e. mortality rates of 10% versus 19%, respectively, in the control group at 6 months after index discharge. In our study, a thorough intervention conducted close to the patient, including medicines reconciliation both at admission and discharge as well as improved

information at discharge to ensure continuous treatment and increase adherence, may constitute characteristics of the intervention important for the effect on survival. Clinical pharmacists performing the procedures of the intervention in close collaboration with the patient, physician and other members of the treatment team are most likely also important for obtaining the effect on survival. At last, the longer follow-up in the present study, prolonged by several months compared to the other RCTs[40, 43], could have allowed prophylactic drugs added during medicine reviews enough time to achieve beneficial effects[22] and probably contributes to explain the intervention`s effect on survival.

Heterogeneity in the pharmacist-led in-hospital interventions, including various elements of various intensity, make comparisons of results amongst studies, as well as interpretation of results, challenging.[22, 44] Furthermore, such interventions are indisputably complex, and evaluating such interventions is complicated.[45, 46] The intervention consists of various components delivered as an overall intervention. With such a design, it is not known whether the overall intervention or only parts of it are important for effect. The intervention in the current study consisted of elements of the highest level of intensity, i.e. diamond level medicines reconciliation[44, 47] and advanced medicines reviews.[48] In the recent RCT from Denmark, a similar intervention of similar intensity reduced emergency department visits and hospital readmissions but did not have an effect on mortality[43], i.e. the opposite of our results. Differences in eligibility criteria, nuances in the delivered intervention and/or care delivered to control patients, clinical pharmacists` training and how they interacted with the rest of the multidisciplinary treatment team may be factors contributing to explain this. The current study nevertheless adds to the international body of literature that high-intensity, in-hospital pharmacist-led interventions to tailor drug therapy may improve clinical outcomes in high-risk patients.

The intervention had no effect on the length of stay (LOS) of the first readmission. This was not surprising, as hospitals in Norway for several years have received incentives to reduce LOS, illustrated by as short as 6 days median LOS of the first readmission in the present study. In comparison, an IMM-intervention showed a reduction from 13.1 days to 9.7 days LOS of the first readmission in Northern Ireland.[23] The number of unplanned hospitalizations during 12 months follow-up did not differ between the groups in the present study, in line with findings by Gillespie et al.[40]

Drug counts were chosen as the preferred multimorbidity measure at patient inclusion, which could be seen as a limitation. Nonetheless, this strategy resulted in the inclusion of a multimorbid patient population, as validated by diseases counts according to the generally accepted definition.[3] Our study included patients from a single hospital in Norway which may challenge the generalizability. However, the study had few exclusion criteria, thus comprising a broad population. The low drop-out rate further contributes favourably to external validity.

It was not feasible to blind participants, study pharmacists or ward physicians to group allocation. To limit bias, the study was blinded on all steps considered possible to blind. Any spill-over effect of the intervention to control patients would, in any case, reduce the effect estimate. Due to the complexity of the intervention a proportion of the intervention patients did not receive the complete intervention, which may also have contributed to the non-significance on the primary endpoint and an underestimation of the effect on survival. The broad inclusion criteria may have resulted in the inclusion of participants at low risk of readmission and death, which might also have contributed to the non-significant result on the primary endpoint, as well as buffered the effect of the intervention on survival. Studying

the effect of pharmacist-led medicines management in a subgroup of multimorbid patients at the highest risk of readmission, e.g. by stratifying on frailty, could be useful. The randomized controlled design and the long follow-up of all patients are factors that strengthen the study.

CONCLUSION

Pharmacist-led medicines management in-hospital to multimorbid patients had no statistically significant effect on time until readmission or death. A statistically significant increase in overall survival was seen. As a response to the increasing challenges of providing safe and evidence-based healthcare to high-risk multimorbid patients, further studies should be conducted to investigate the effect of such an intervention on a larger scale.

Competing interests statement

Author ML received Ph.D. funding from the South-Eastern Norway Regional Health Authority (grant number 12/00718). The other authors declare that they have no competing interests.

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for the positive attitude to the study, and finally Dominic Anthony Hoff for valuable support regarding data punching.

Data sharing statement

The data that support the findings of this study are available from Oslo University Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Deidentified participant data are however available from the authors upon reasonable request and with permission of Oslo University Hospital, with publication. Additional related documents, e.g. patient consent forms, are available at request.

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Author contributions

Marianne Lea: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing

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Disclaimer: Data from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

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FIGURE LEGENDS

Figure 1. Title: Graphical depiction of the study design, inspired by Perera and colleagues [29].

Objects are represented by squares and activities by circles.

Figure 2. Title: Patient flow.

Figure 3

a) Title: Time to first hospital readmission or death in the intervention versus the control group.

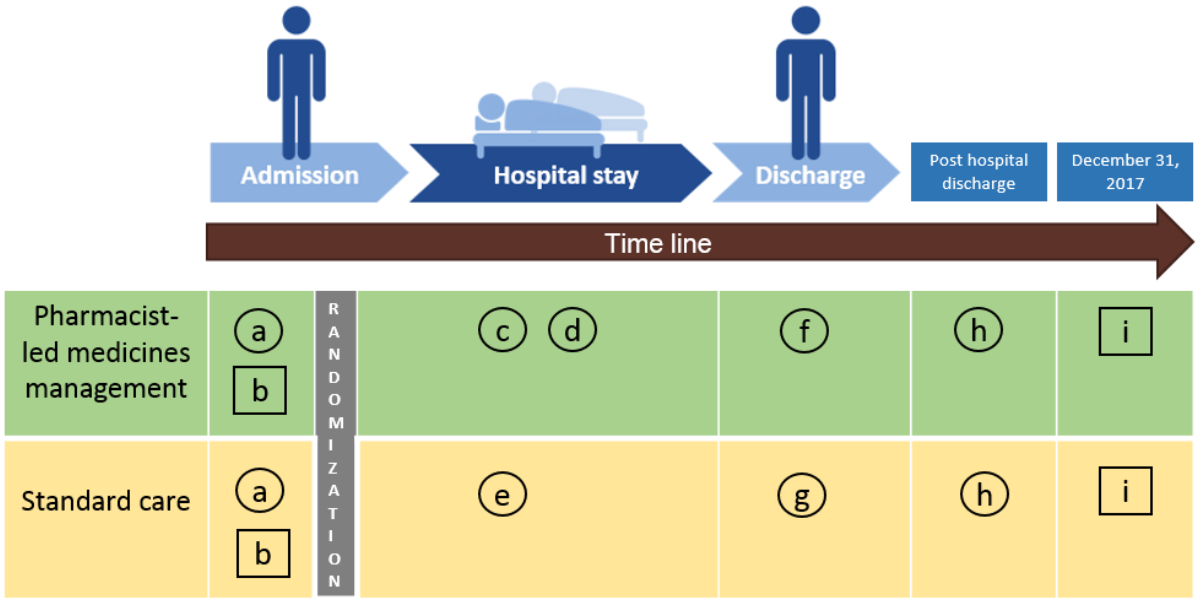
b) Title: Overall survival in the intervention versus the control group.

SUPPLEMENTARY MATERIAL

S1 Appendix. Original trial protocol, protocol amendments, statistical analysis plan, statistical analysis plan amendment and timeline of the study with milestones.

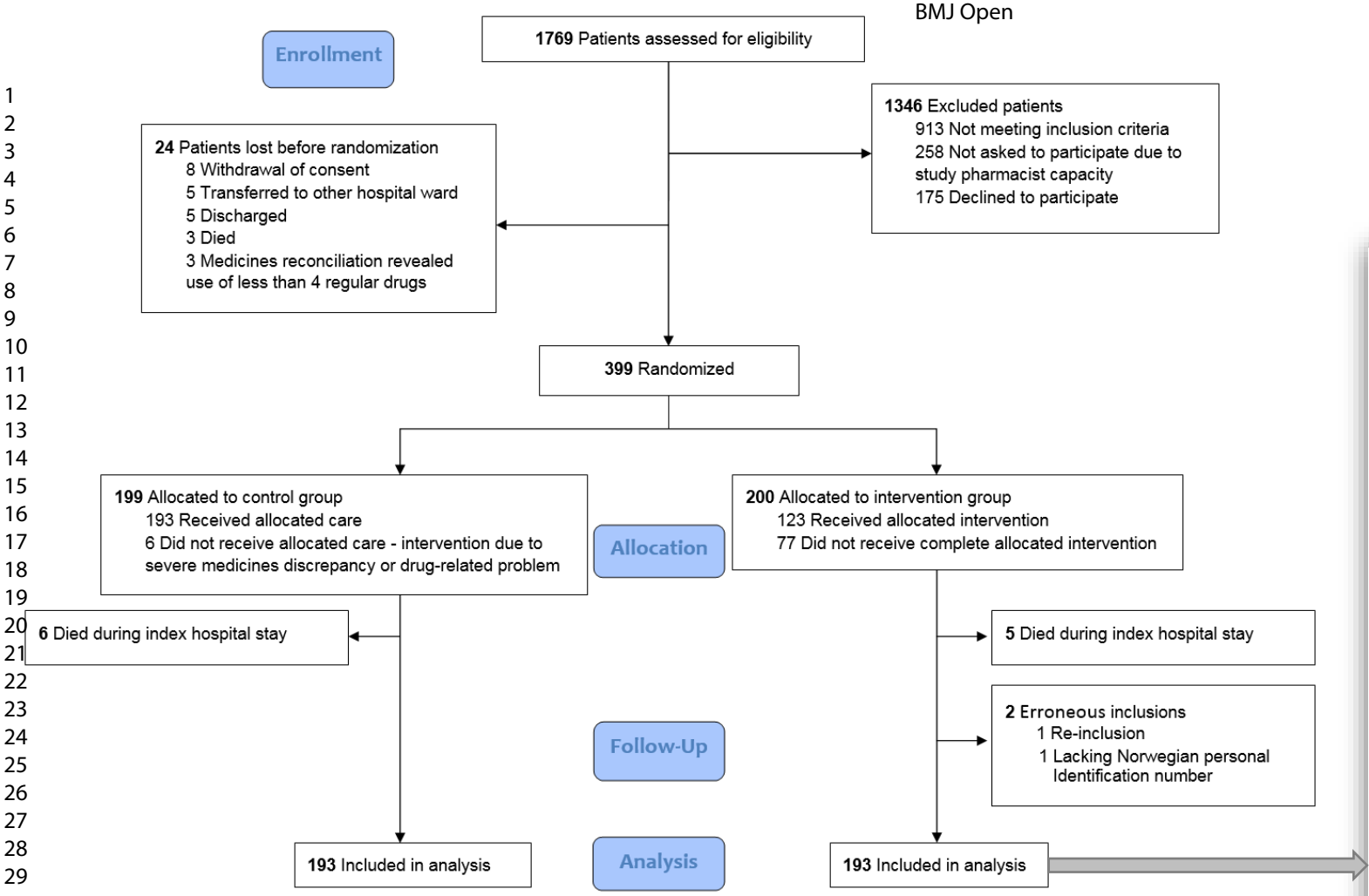
S2 Appendix. CONSORT Checklist.

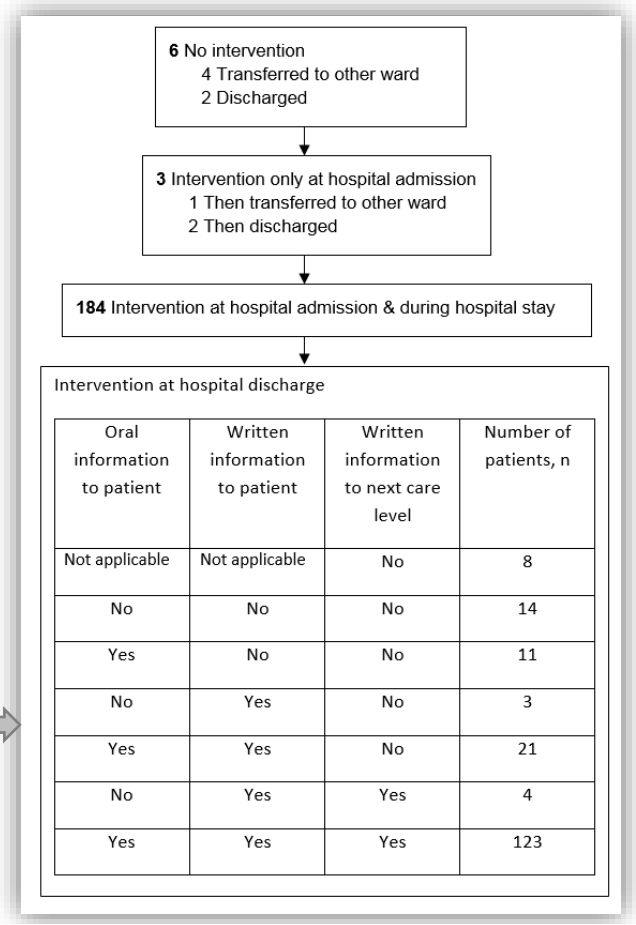
S3 Appendix. Time to first hospital readmission in the intervention versus the control group, censored for deaths.



(a)	Medicines reconciliation and review conducted by clinical pharmacist *without* discussion of medicine discrepancies or drug-related problems (DRPs) and possible solutions in the multidisciplinary team[a]
[b]	Patient characteristics collected
(c)	Multidisciplinary treatment team[a] discussions of medicine discrepancies and DRPs revealed at hospital admission and possible solutions
(d)	Medicines review conducted by clinical pharmacists by systematically addressing 11 pre-defined risk categories for each drug each patient was prescribed at a given point of time; drug monitoring, adverse effect, drug-drug interaction, non-optimal drug therapy, reduced organ function/contraindication, inappropriate drug in elderly, unnecessary drug, course length, practical problem, adherence issue and other. Medicines reviews were performed at admission and repeatedly as needed due to changes in either prescription, patient symptoms, clinical state, and/or laboratory values. Patients were reviewed for such changes daily, Monday to Friday, during regular daytime working hours. Consecutively multidisciplinary treatment team[a] discussions of identified DRPs and possible solutions.
(e)	Standard in-hospital care provided by physicians with internal medicine expertize, nursing staff and when needed; clinical nutrition physiologists and/or physiotherapists
(f)	Medicines reconciliation, followed by written and verbal information tailored to the patient`s further needs of care, as well as discharge activities aiming to ensure continuous treatment and increase adherence: • Written systematic information comprising a reconciled drug list with description and justification for all changes made during the hospital stay, to the next care provider[b] (all patients), and to the patient/relative if they to some extent would be involved in handling the drugs after discharge • Verbal information/conversation with the patient and/or relative adapted to the patient needs[c] - if they to some extent would be involved in handling the drugs after discharge • Assistance with retrieving drugs from the pharmacy, if needed • Providing the patient with drugs from the hospital pending on an updated multidose delivery, if needed
(g)	Discharge medicine information (not standardized) provided by physicians with internal medicine expertize and nursing staff
(h)	Standard care in the primary health care (details not collected)
[i]	Last day of follow-up on readmissions and mortality outcomes

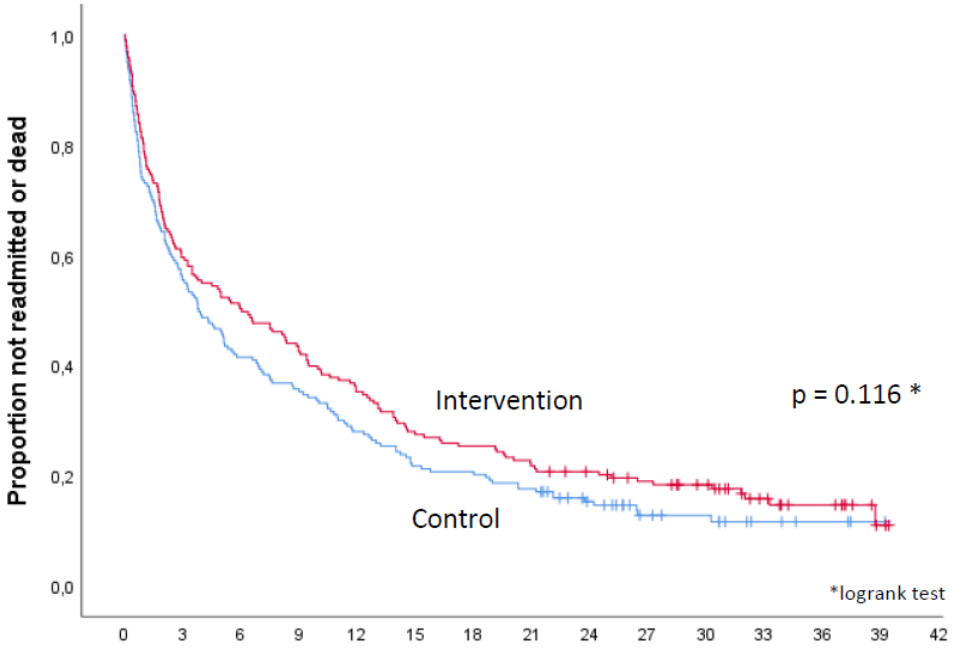
[a] The multidisciplinary treatment team consisted of physician with expertise in internal medicine, nursing staff, clinical pharmacist, and when needed; clinical nutrition physiologists and/or physiotherapists
[b] The general practitioner, nursing home, home nurse and/or multidose delivering pharmacy.
[c] Sometimes regarding the entire drug list, sometimes the most important changes, sometimes regarding one specific drug. If the patient was considered to benefit from any provided information or given the opportunity to ask questions, such a targeted conversation was conducted, even if a complex conversation was not considered favorable.





Oral information to patient	Written information to patient	Written information to next care level	Number of patients, n
Not applicable	Not applicable	No	8
No	No	No	14
Yes	No	No	11
No	Yes	No	3
Yes	Yes	No	21
No	Yes	Yes	4
Yes	Yes	Yes	123

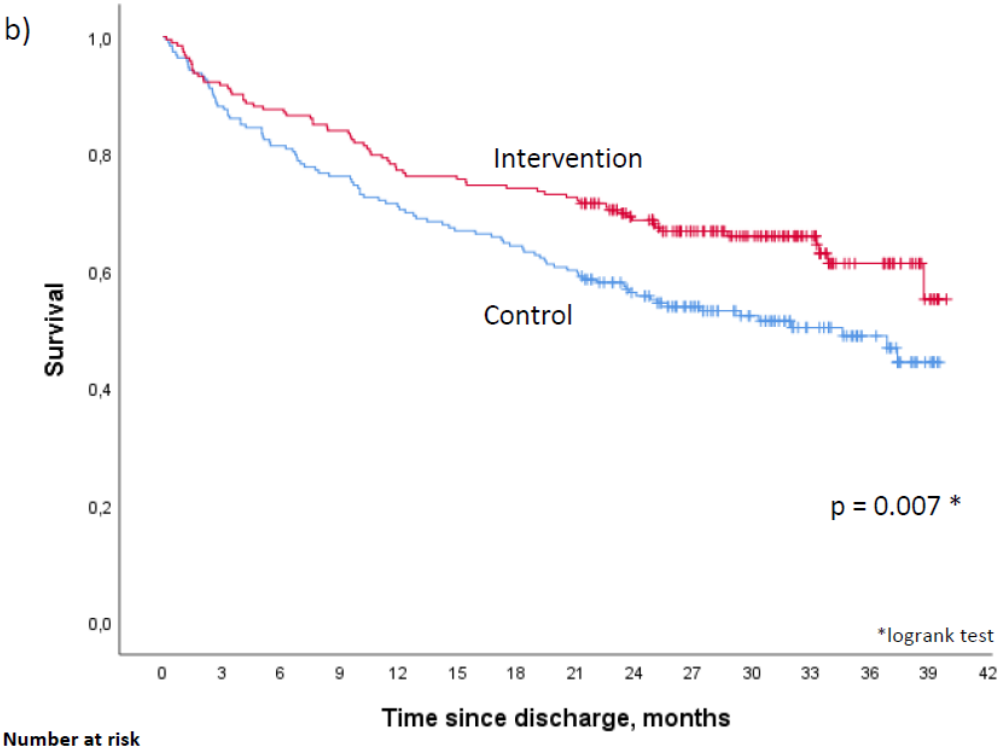
a)



Number at risk

Intervention	193	115	97	82	68	53	49	42	37	31	26	15	10	2
Control	193	107	80	69	54	42	40	34	23	13	11	5	3	1

b)



Number at risk

Intervention	193	177	169	162	149	146	143	140	115	93	73	49	27	8
Control	193	170	157	147	137	129	124	116	97	76	59	40	25	7

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

Project leader and co-supervisor: Associate professor at University of Oslo, Norway, Head of the internal medicine ward at Oslo University Hospital, Norway, MD, PhD Morten Mowe, mormow@ous-hf.no

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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.

Contents

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

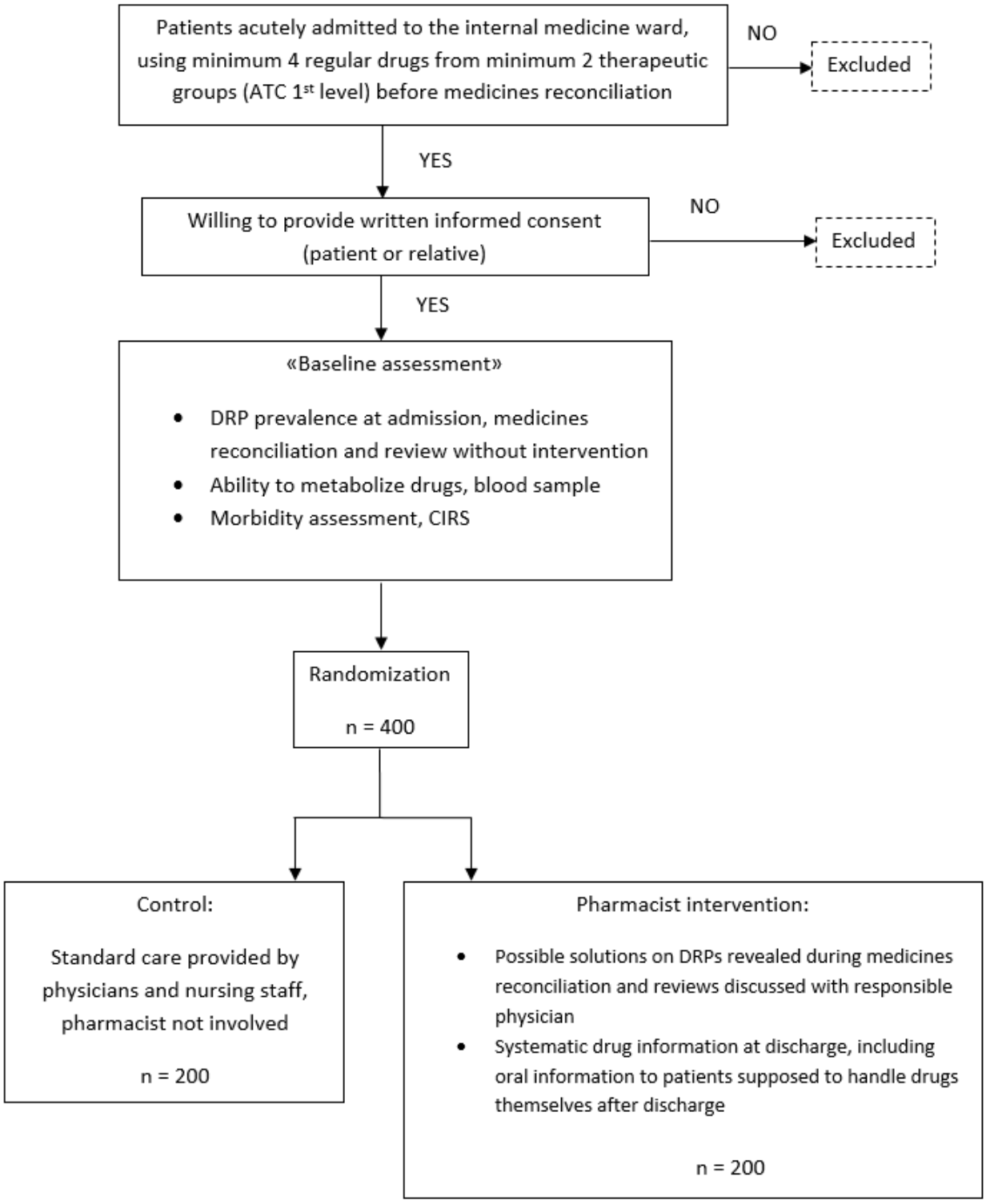

Figure 1. Overview over how the study will be conducted.
ATC = Anatomical Therapeutic Chemical, DRP = drug-related problems, CIRS = Cumulative Illness Rating Scale.

”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.

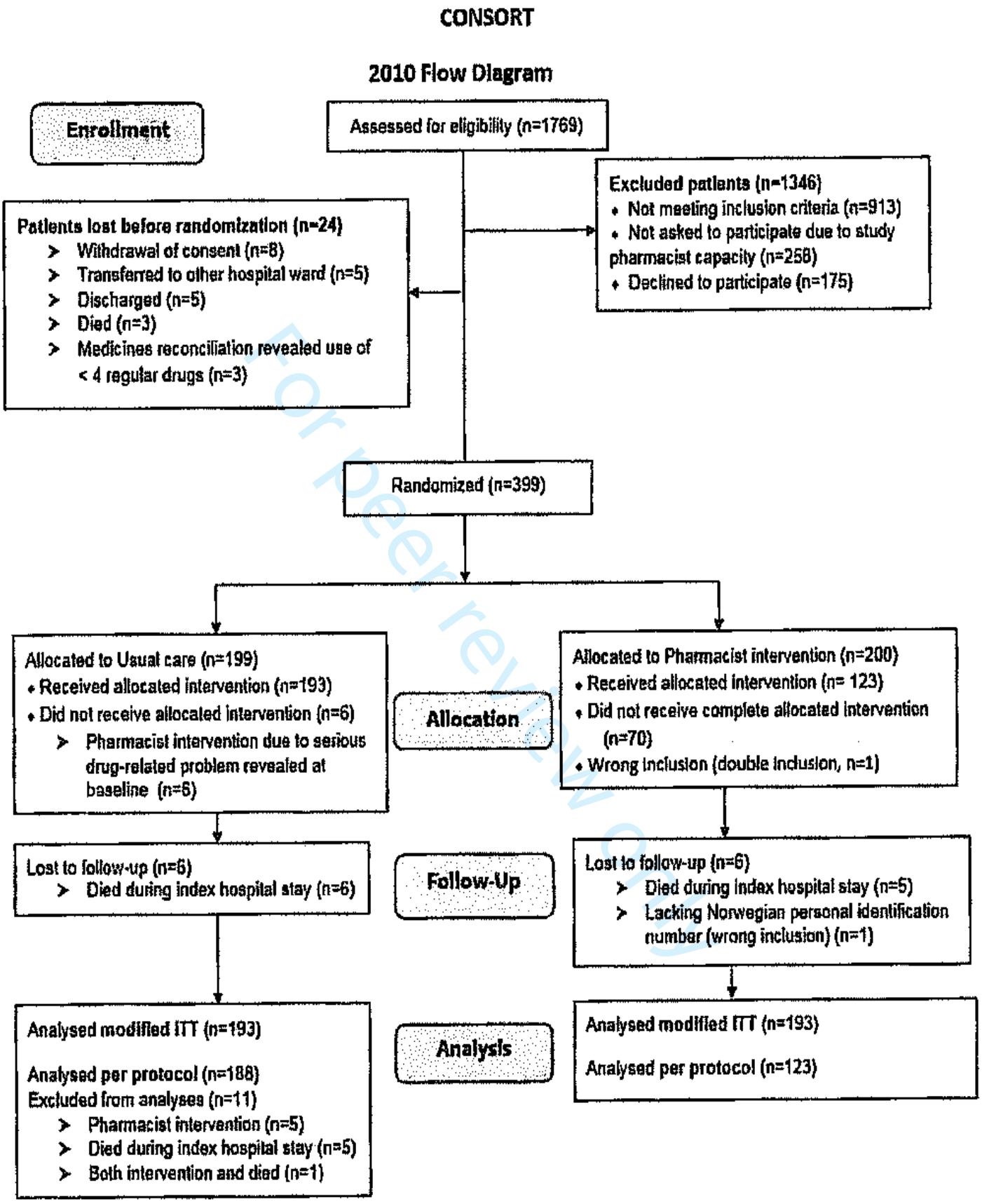
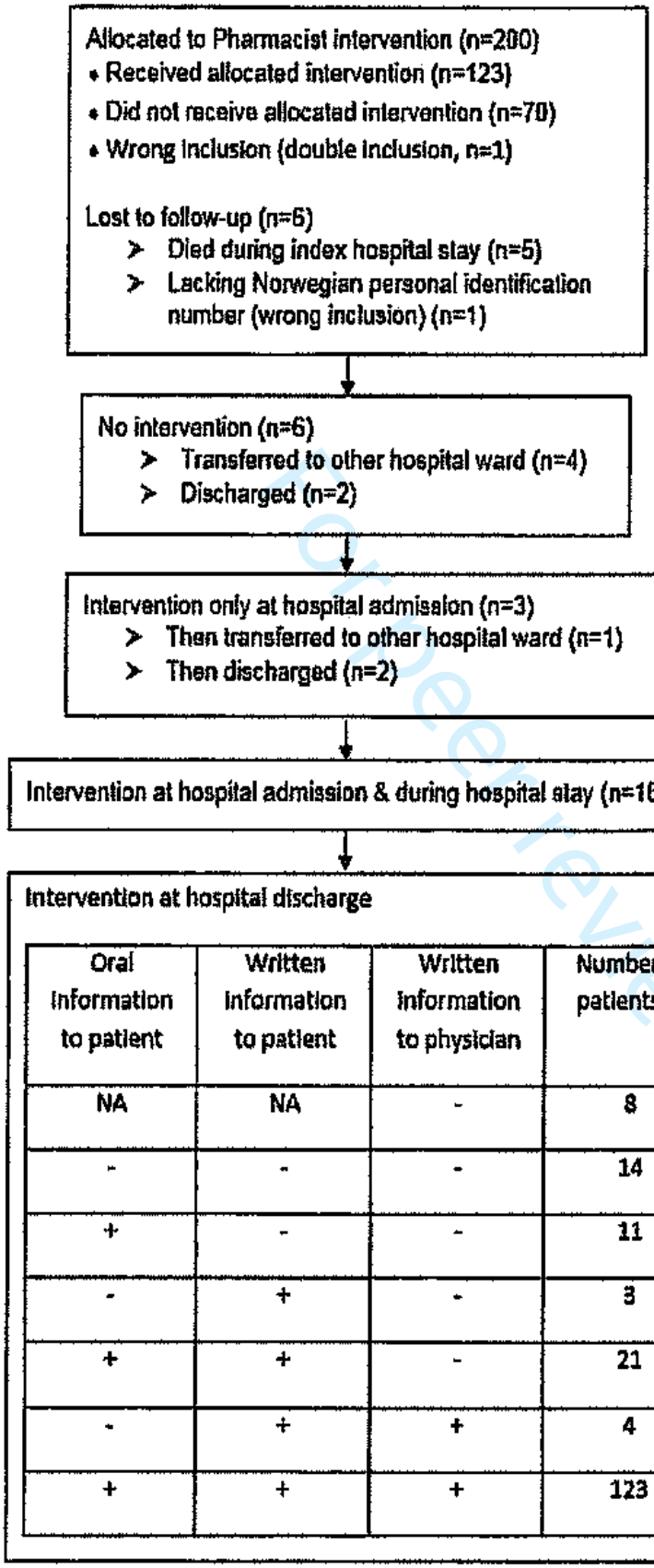


Figure 1. Patient flowchart. ITT = intention to treat.



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
Main supervisor
University of Oslo

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.

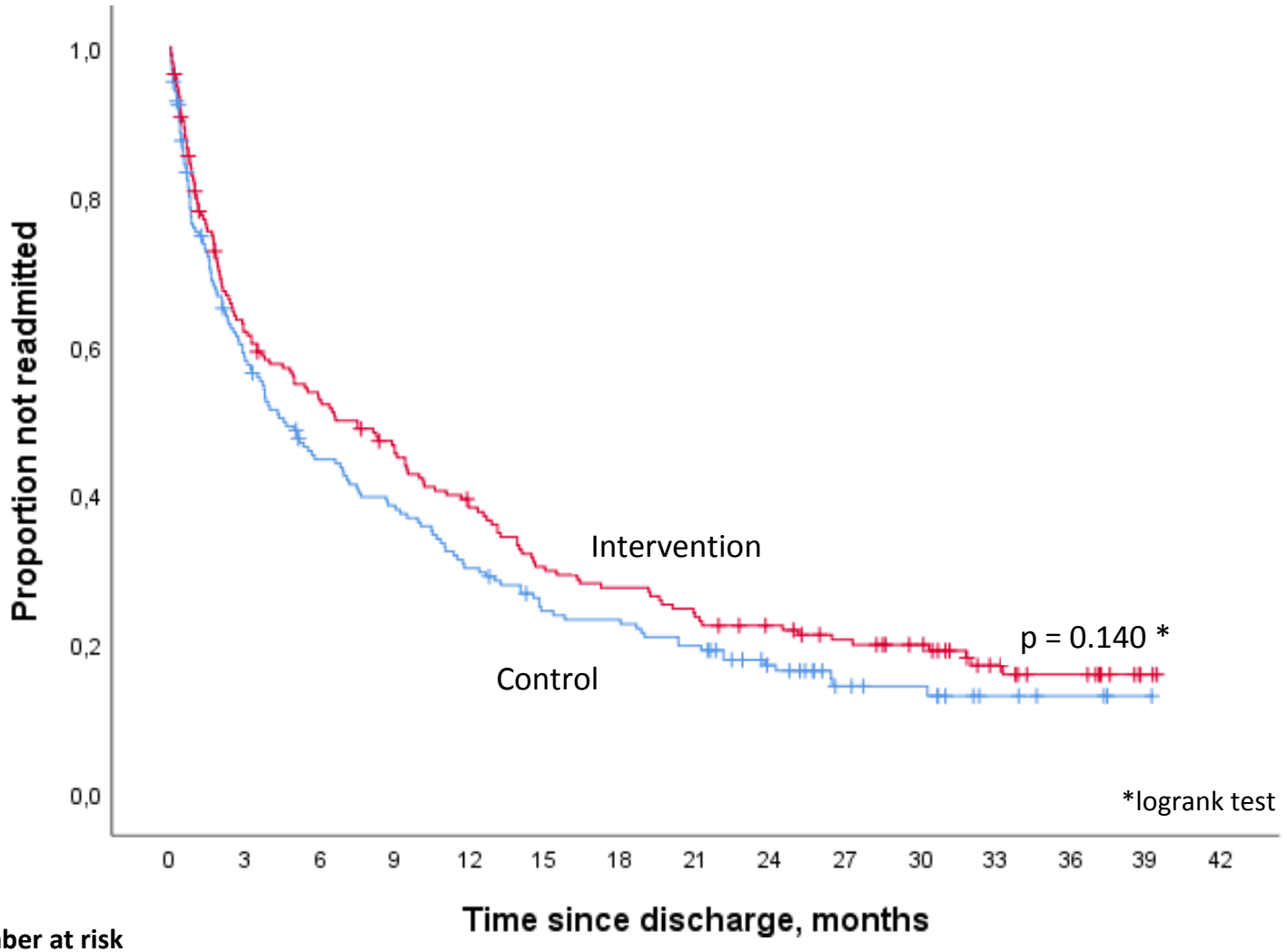
**Huge workload at the Registers entails a very long processing time for outcome data.

CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial[a]

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.



Number at risk

Intervention	193	115	97	82	68	53	49	42	37	31	26	15	10	2
Control	193	107	80	69	54	42	40	34	23	13	11	5	3	1

BMJ Open

Effect of medicines management versus standard care on readmissions in multimorbid patients: A randomized controlled trial

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Date Submitted by the Author:	23-Nov-2020
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Secondary Subject Heading:	Medical management, Pharmacology and therapeutics, Public health
Keywords:	Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, INTERNAL MEDICINE, PUBLIC HEALTH, THERAPEUTICS, CLINICAL PHARMACOLOGY

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TITLE PAGE

TITLE

Effect of medicines management versus standard care on readmissions in multimorbid patients: A randomized controlled trial

AUTHORS

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WORD COUNT: 3785

CATEGORY: Original research

ABSTRACT

Objective: To investigate the effect of pharmacist-led medicines management in multimorbid, hospitalized patients on long-term hospital readmissions and survival.

Design: Parallel-group, randomized controlled trial.

Setting: Recruitment from an internal medicine hospital ward in Oslo, Norway. Patients were enrolled consecutively from August 2014 until the predetermined target number of 400 patients. The last participant was enrolled March 2016. Follow-up until December 31, 2017, i.e. 21-40 months.

Participants: Acutely admitted multimorbid patients ≥ 18 years, using minimum four regular drugs from minimum two therapeutic classes. 399 patients were randomly assigned, 1:1, to the intervention or control group. After excluding 11 patients dying in-hospital and 2 erroneously included, the primary analysis comprised 386 patients (193 in each group) with median age 79 years (range 23-96) and number of diseases 7 (range 2-17).

Intervention: Intervention patients received pharmacist-led medicines management comprising medicines reconciliation at admission, repeated medicines reviews throughout the stay and medicines reconciliation and tailored information at discharge, according to the Integrated Medicines Management (IMM) model. Control patients received standard care.

Primary and secondary outcome measures: The primary endpoint was difference in time to readmission or death within 12 months. Overall survival was a priori the clinically most important secondary endpoint.

Results: Pharmacist-led medicines management had no significant effect on the primary endpoint time to readmission or death within 12 months (median 116 versus 184 days, HR

0.82, 95% CI 0.64 to 1.04, p=0.106). A statistically significantly increased overall survival was observed during 21-40 months follow-up (HR 0.66, 95% CI 0.48 to 0.90, p=0.008).

Conclusions: Pharmacist-led medicines management had no statistically significant effect on time until readmission or death. A statistically significant increased overall survival was seen. Further studies should be conducted to investigate the effect of such an intervention on a larger scale.

Trial Registration: ClinicalTrials.gov-Identifier:NCT02336113, closed for new participants.

ARTICLE SUMMARY

Strengths and limitations of this study

- Randomized controlled design, blinded in the steps possible to blind
- Included almost 200 high-risk multimorbid patients in each group and followed them for 20-41 months
- Hard endpoints, readmissions and mortality, collected from national registers
- Inclusion from a single hospital in Norway
- Spill-over effect may have reduced the effect estimate

KEYWORDS: multimorbid patients, integrated medicines management, pharmacist-led, internal medicine, hospital readmissions, survival

INTRODUCTION

Increased life expectancy and steadily improving healthcare contribute to a growing subpopulation of multimorbid patients, commonly defined as having a minimum of two conditions.[1-3] The prevalence of multimorbidity is reported to be 20-30% in the general population, 55-98% in the elderly and 22-65% in hospitalized patients.[4-6] Multimorbidity is associated with the use of multiple drugs, increased use of healthcare services and reduced life expectancy.[3, 7-9] The organization of healthcare services and treatment guidelines is however mainly focused on single diagnoses, while coexisting diagnoses or use of multiple drugs are rarely taken into account.[10, 11] Studying the care of multimorbid patients is crucial to managing the future global challenge of ensuring safe, effective and evidence-based care to these patients.[1, 11, 12]

Multimorbid patients using numerous drugs are at high risk of harm by drug-related problems (DRPs).[13, 14] DRPs are reported to cause 10-30% of all hospital admissions, whereof a high proportion is preventable.[15-17] Drugs also cause problems during the hospital stay[18, 19], which pose a risk of readmissions.[20, 21] A recent Cochrane review found no evidence that medicines reviews reduce hospital readmissions or mortality.[22] The authors state that important effects may have been overlooked due to short follow-up in included studies, and request high-quality studies with long follow-up in high-risk patient populations.[22]

The Integrated Medicines Management (IMM) model has been established as a tool for clinical pharmacists to optimize and individualize drug therapy.[23] IMM comprises a systematic approach to ensure high quality of the use of drugs throughout the hospital stay, comprising a three-step procedure, i.e. medicines reconciliation at admission, medicines

reviews during the stay and medicines reconciliation and -information at discharge.[23-27] Nevertheless, only a very limited number of clinical pharmacists are working in Norwegian hospitals, hence standard care for hospitalized patients does not include IMM or other services by clinical pharmacists. Several studies have investigated the effect of implementing either parts of, or the complete IMM model on different efficacy measures[23-25, 28], but to our knowledge, not in multimorbid patients. The objective of the present study was to investigate the effect of pharmacist-led medicines management in multimorbid, hospitalized patients on long-term hospital readmissions and survival.

MATERIALS AND METHODS

Study Design

This parallel-group, randomized controlled trial, approved by the Regional Committee for Medical and Health Research Ethics (2014/704/REK south-eastern D) and the Privacy Ombudsman, was conducted at the internal medicine ward, Oslo University hospital (Ullevaal), Norway. The ward comprised 24 beds and mainly received patients with multiple medical issues, in particular hematological, endocrine, infectious and/or cardiovascular. Patients were considered for inclusion Monday to Friday during regular daytime working hours, from August 30, 2014, until the predetermined target number of 400 patients was enrolled. Eligible patients were prospectively invited and enrolled in the study following written informed consent. S1 Appendix shows the original trial protocol, protocol amendments, the statistical analysis plan and the timeline of the study with the milestones. S2 Appendix shows the CONSORT Checklist. Figure 1 gives a graphical depiction of the study design, as suggested for studies of complex interventions.[29]

The trial was registered in ClinicalTrials.gov, identifier: NCT02336113, in June 2014. Due to a minor Protocol Registration and Results System (PRS) review comment, the trial was first published on their website in January 2015. A clarification that readmission data were to be harvested from the Norwegian Patient Registry, was the only addition to the original registration. The trial is closed for new participants.

Participants

Inclusion criteria were: acute admission, age ≥ 18 years and use of at least four regular drugs from minimum two therapy classes (Anatomical Therapeutic Chemical (ATC)[30] at 1st level) at admission. The latter was chosen as the preferred multimorbidity measure[31], as drug counts were considered more reliable than disease counts in the acute hospital admission setting. Drugs were counted before medicines reconciliation. However, if the medicines reconciliation revealed that this inclusion criterion was not fulfilled, the patient was excluded from the study. Exclusion criteria were i) terminally ill, ii) isolated due to severe infections or iii) unable to communicate in Norwegian or English and no translator available. Patients readmitted during the study period were not invited for 'a second' inclusion.

Randomization and blinding

The patients were randomized 1:1 to the intervention or control group. Centre for Biostatistics and Epidemiology, Oslo University Hospital, was responsible for the randomization procedure. Their staff had no contact with patients, study pharmacists or ward staff. A random number generator program and a permuted block design were used to generate the randomization sequence, which was delivered to the study pharmacists in sequentially numbered, opaque, sealed envelopes. The investigators were blinded to block size, which was randomly varied. Randomization took place following patient inclusion and

baseline assessments. A study pharmacist assigned the envelope with the lowest number to the individual participant and signed the allocation before the envelope was opened.

It was neither feasible to blind participants nor study pharmacists to the allocation. It was also known by ward staff which of the patients belonged to the intervention group. Ward staff was, however, unable to distinguish between patients randomized to the control group and patients not participating in the trial. The primary endpoint analysis was conducted on a blinded dataset (by researchers who did not see patients). The staff from the Norwegian Patient Registry and the Norwegian Cause of Death Registry providing outcome data were not involved in data collection or preparation of data files and were blinded to group allocation.

Data collection and baseline assessments

During the inclusion period, six clinical pharmacists, all with a master`s degree in clinical pharmacy and standardized training in IMM, collected data, conducted baseline assessments and provided the various steps of the intervention. All steps were standardized using translated IMM procedures adapted to the Norwegian hospital setting.[23-27, 32] A DRP was defined according to the Pharmaceutical Care Network Europe (PCNE) as *"an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"*.[33]

Blood samples were collected for biochemical analyses. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula[34], except for obese patients (body-mass index > 30), for whom the Salazar-Corcoran formula was used.[35] An experienced senior physician retrospectively collected information from medical records to calculate the Charlson Comorbidity Index (CCI) score.[36]

Before allocation, baseline assessments were conducted for all included patients, comprising medicines reconciliation and review. The purpose of these baseline assessments was to assess the prevalence of DRPs and drug-related hospitalizations [37]. These medicines reviews included only drugs used before admission, not drugs initiated during transport, or following hospital admission. The pharmacists had access to the patient's medical history and laboratory results up to and including admission time. Importantly though, medicines discrepancies, i.e. mismatches between the reconciled drug list and the list recorded at hospital admission, and DRPs revealed during these baseline assessments were neither discussed in the multidisciplinary treatment team, nor documented in the patient record. Before allocation, the study pharmacist assessed whether any medicines discrepancy or DRP could result in irreversible detrimental effects or death if not handled immediately. If the patient was allocated to the control group, any such issue was discussed with a senior physician (MM) who decided whether it was necessary to intervene.

The intervention group – in-hospital pharmacist-led medicines management

The thorough intervention implied the inclusion of clinical pharmacist(s) in the patients` multidisciplinary treatment team throughout the hospital stay, working in close collaboration with the patient, physicians and other members of the team, as shown in Figure 1. The medicines management process can be divided into three parts covering the patients` hospital stay; medicines reconciliation at admission, medicines review repeatedly during the entire stay and medicines reconciliation and tailored information at discharge.[23-27] Medicines reviews were performed at admission and repeatedly as needed due to changes in either prescription, patient symptoms, clinical state, and/or

laboratory values. Patients were reviewed for such changes daily, Monday to Friday, during regular daytime working hours.

During medicines reviews, a list of pre-defined risk categories, all described in detail in Table 1, were systematically addressed for each drug in each patient. Furthermore, an overall benefit-risk assessment was made with the main goal of tailoring drug therapy to the individual participant, giving significant weight to the patient perspective. Medicines discrepancies and DRPs revealed during both baseline assessments and the hospital stay were discussed in the multidisciplinary treatment team. At discharge, a medicines reconciliation was conducted, followed by written and oral information tailored to the patient's further needs of care, provided to the patient and/or next care provider, see Figure 1. The main goals of this step were to answer drug questions, to ensure continuous treatment, to increase adherence, and to provide the patient and/or next care provider a complete overview of all drugs.

Table 1. Detailed description of the risk categories that were systematically addressed for each drug in each patient during the medicines reviews, and examples of sources used by clinical pharmacists to address them.

Risk category	Detailed description	Examples of sources
Drug monitoring	Need for therapeutic drug monitoring or laboratory monitoring, e.g. digoxin, warfarin, antiepileptics	• The Pharmacology Portal – Norwegian portal for drug and intoxicant analyses - http://www.farmakologiportalen.no/ • Norwegian National Centre for Epilepsy • Centre for Psychopharmacology, Diakonhjemmet Hospital, Norway
Adverse effect	Presence of symptoms or changes in laboratory values possibly caused by drug(s)	• Summary of Product Characteristics (SPC) • UpToDate • Micromedex • CredibleMeds, QTDrugs List, - https://crediblemeds.org/
Drug-drug interaction	Clinically relevant drug-drug interactions	• The Norwegian Medicines Agency – Drug interactions checker • Micromedex – Drug interactions • Drugs.com – Drug interactions checker
Non-optimal drug therapy	Lack of drug treatment or non-optimal drug treatment of a symptom/disease	• Therapy guidelines • BMJ Best Practice • UpToDate • Summary of Product Characteristics (SPC)
Reduced organ function / contraindication	Drug or dosage of drug inappropriate due to reduced kidney function, reduced liver function, contraindications or other diseases.	• The Renal Drug Handbook - https://renaldrugdatabase.com/ • UpToDate • Micromedex • Internetmedicin https://www.internetmedicin.se/searchresult.aspx?search=lever (reduced liver function/drugs that can harm the liver) • Summary of Product Characteristics (SPC)
Inappropriate drug in elderly	Use of less favourable drug in patients over 65 years old, e.g. anticholinergics	• STOPP 2 (Screening Tool of Older Persons' Prescriptions) • Beers criteria
Unnecessary drug	Drug in use is not indicated	• Therapy guidelines • Summary of Product Characteristics (SPC) • UpToDate
Course length	Consideration of appropriate duration of course length, e.g. duration of antibiotics	• Summary of Product Characteristics (SPC) • The Norwegian Directorate of Health – National guideline for the use of antibiotics in hospitals • The European Committee on Antimicrobial Susceptibility Testing - EUCAST - minimum inhibitory concentrations
Practical problem	Practical challenges in drug handling, e.g. inhalation devices	• Summary of Product Characteristics (SPC) • Local procedure for tablets and capsules - dividing, opening and crushing • Handbook of Drug Administration via Enteral Feeding Tubes - https://about.medicinescomplete.com/publication/drug-administration-via-enteral-feeding-tubes/
Adherence issue	Patient does not, intentionally or unintentionally, use / take drug as agreed	• Quick guide inhalators - https://sykehusapoteket.no/Documents/Inhalasjonsmedisin%20for%20sykehusleger.pdf • Videos – use of inhalators - https://www.felleskatalogen.no/medisin/bruk-av-inhalatorer/aerochamber
Other	Problem not applicable in other subgroups, e.g. prescription errors, documentation errors	• The patient`s medical record

The control group - standard care

The control group received standard care, see Figure 1, which in line with standard procedures in Norwegian hospitals included neither medicines reconciliation nor medicines reviews or any other service from clinical pharmacists. Medicines discrepancies and DRPs revealed during baseline assessments in control patients were only registered in the research database, and not discussed in the multidisciplinary treatment team.

Endpoints

The primary endpoint was time to first hospital readmission or death within 12 months after discharge.

Secondary endpoints:

- Overall survival
- Number of unplanned hospitalizations per patient within 12 months after discharge
- Proportion of patients:
    - with unplanned hospitalizations within 30 days, 6 months and 12 months after discharge
    - who died within 30 days, 6 months, 12 months and 20 months after discharge
    - who died or had unplanned hospitalizations within 30 days, 6 months and 12 months after discharge
- Length of stay (LOS) of first hospital readmission
- Time to the first unplanned readmission within 12 months after discharge, censored for deaths

In the original trial protocol, included in S1 Appendix, the *difference between the control and intervention group in time to the first readmission* was defined as the primary endpoint without further specification. As death is a competing risk to readmissions, it was considered appropriate to use the *difference in time to readmission or death* as the primary endpoint. This was clarified in the statistical analysis plan, which was finalized and signed before outcome data files were available.

Data on readmissions were provided by the Norwegian Patient Registry and data on mortality by the Norwegian Cause of Death Registry. We had originally planned a follow-up of 12 months. However, as both the inclusion period and the retrieval of outcome data took longer than planned, we decided to extend the follow-up of all patients to December 31, 2017, to increase statistical power. This amendment was described in the statistical analysis plan, which was finalized and signed before any outcome data files were available. Because the inclusion period lasted approximately 1.5 years, the follow up of each individual patient was in the range 21 – 40 months.

The primary efficacy analysis was a modified intention to treat-analysis excluding patients who died during the index hospital stay as they were never at risk for readmission, as well as erroneously included patients. The analysis population was defined before outcome data files were received.

Sample size

The sample size calculation was based on an expected 12-month readmission frequency of 50%.[23] It was estimated that to detect a 15% absolute reduction in hospital readmissions with 80% power and a significance level of 5%, we would need 168 patients in each group. To compensate for any dropouts, it was decided to enroll 200 patients in each group. Sample

size calculations based on proportions are generally considered reliable for survival analysis, but might in some instances overestimate the required sample size.[38] In other words: since a survival analysis utilizes the information better than a comparison of proportions at a given time, the power will be somewhat higher than estimated above.

Statistics

Time-to-event endpoints were compared between groups by the Kaplan Meier method and the log-rank test. Cox's proportional hazards model was applied to estimate hazard ratios (HRs), which are presented with 95% confidence intervals (CIs). The proportionality assumption was checked by visual inspection of log(-log) plots. Continuous variables were compared between the two groups using Mann-Whitney tests. In an additional sensitivity analysis of time to readmission, which was not included in the statistical analysis plan, death was treated as a competing risk using the Fine and Gray method [39].

Statistical analyses were performed by IBM SPSS Software version 25.0 (IBM Corp. NY) and STATA 16. P values < 0.05 were regarded as statistically significant.

Patient and Public Involvement

During the planning of the study, patient representatives from the medical clinic participated in the preparation of the patient information leaflet and provided input on the study design, e.g. the choice of the primary endpoint.

RESULTS

During the study period, August 30, 2014, to March 17, 2016, 2174 patients were admitted to the internal medicine ward and 1769 (81%) were assessed for eligibility. Figure 2 shows the patient flow. Among the 598 patients invited to participate, 175 (29%) declined

(permission to register reasons for declining not obtained). 399 patients were randomized, 200 to the intervention group and 199 to the control group. Following randomization, 11 patients (5 intervention and 6 control) who died during the hospital stay and 2 patients (both intervention) who were erroneously included, were excluded from the analyses. Thus, the analysis population for all endpoints comprised 193 patients in each group, all followed-up until December 31, 2017, i.e. for a minimum of 21 months and a maximum of 40 months.

The median age in the analysis population was 79 years (range 23-96), 356 (92%) were home-dwelling before hospitalization and 213 (55%) were women. The median number of regular drugs at hospital admission was 8 (range 4-19). The median number of diseases was 7 (range 2-17) and the median CCI score was 3 (range 0-12). The median number of DRPs per patient identified during baseline assessments was 13 (range 3-42). The baseline characteristics of the patients in the control versus the intervention group are presented in Table 2. No differences of importance were observed between the groups.

Table 2. Characteristics of patients in the analysis population.

Characteristic	**Control (n=193)**	**Intervention (n=193)**
Women	106 (55%)	102 (53%)
Age	80.7 (23.1-96.4)	78.0 (25.7-95.6)
Number of unplanned hospitalizations last 6 months	1 (0-6)	0 (0-11)
Charlson Comorbidity Index score	3 (0-12)	2 (0-11)
Most frequent medical history:		
• Hypertension	91 (47%)	108 (56%)
• Endocrine and metabolic diseases	77 (40%)	80 (42%)
• Kidney disease	63 (33%)	73 (38%)
• Congestive heart failure	81 (42%)	68 (35%)
• Arrhythmia	72 (37%)	71 (37%)
Body-mass index[a]	24.4 (14.4-48.4)	25.0 (13.1-43.3)
Laboratory results:		
• Glomerular filtration rate (ml/min)	49 (8-235)	52 (9-229)
• Serum-albumin (g/L)[b]	38 (24-51)	38 (22-56)
• C-reactive protein (nmol/L)	133 (0-3419	152 (0-5248)
Number of prescribed drugs[c] at hospital admission:		
• Regular	8 (4-19)	8 (4-19)
• On demand	2 (0-10)	2 (0-11)
Assistance with drug administration before hospitalization:		
• Multidose	51 (26%)	46 (24%)
• Home nurse	33 (17%)	28 (15%)
• Nursing home	15 (8%)	15 (8%)
• Relative	13 (7%)	14 (7%)
Home-dwelling before hospitalization	178 (92%)	178 (92%)
Number of drug-related problems	13 (3-31)	13 (3-42)
Length of index hospital stay, number of days	8 (2-57)	7 (1-66)
Total number of prescribed drugs at hospital discharge	11 (3-24)	11 (3-23)
Discharged to home	124 (64%)	129 (67%)
Assistance with drug administration after discharge:		
• Multidose	28 (15%)	26 (14%)
• Home nurse	32 (17%)	21 (11%)
• Nursing home	51 (26%)	51 (26%)
• Relative	7 (4%)	11 (6%)
• Other institution/hospital ward	18 (9%)	13 (7%)

Data are n (%) or median (range).

[a] Body-mass index was registered for 144/193 control patients and 148/193 intervention patients.

[b] Serum-albumin was registered for 181/193 control patients and 187/193 intervention patients.

[c] After medicines reconciliation

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In the group receiving pharmacist-led medicines management, a total of 3826 DRPs were revealed at hospital admission and during the hospital stay. Type of DRPs revealed and presented for discussion in the multidisciplinary team and the respective acceptance rates will be presented in a separate publication. In overall numbers, 1100 of the 3826 identified DRPs (29 %) were solved without the need for discussion in the multidisciplinary treatment team, while 1075 (28%) were not prioritized for discussion, i.e. considered of low importance compared to other DRPs or the patients` clinical state. The remaining 1651 (43 %) DRPs were discussed in the multidisciplinary team, whereof 1022 (62 %) led to immediate changes in the individual patient's drug treatment. In 6 of the 193 control patients (1.5 %) severe medicines discrepancies or DRPs that had to be intervened on were revealed during baseline assessments.

Figure 3a shows time to first readmission or death in the two groups. The median time to readmission or death was 184 days in the intervention group and 116 days in the control group, but the difference was not statistically significant (HR 0.82, 95% CI 0.64 to 1.04, p=0.106). Sensitivity analyses, extending follow-up until December 31, 2017, or excluding control patients who were intervened on, did not influence the effect estimate (HR 0.84, 95% CI 0.68 to 1.05, p=0.118 and HR 0.85, 95% CI 0.68 to 1.06, p=0.149, respectively). The secondary endpoint analysis of time to first readmission, censoring for 20 deaths, gave a similar effect estimate (HR 0.81, 95% CI 0.63-1.04, p=0.104), shown in S3 Appendix. When death was instead treated as a competing risk the subdistribution hazard ratio was SHR 0.83, 95%CI 0.64-1.06, p=0.137.

There was a statistically significant difference in overall survival (HR 0.66, 95% CI 0.48 to 0.90, p=0.008), as shown in Figure 3b. The results of other the secondary endpoint analyses

are shown in Table 3. Within 20 months after the index discharge, 27% of the intervention patients had died versus 39% of the control patients.

Table 3. Secondary endpoint analyses.

Endpoint	Intervention group (n=193)	Control group (n=193)	p value
Number of unplanned hospitalizations per patient within 12 months after discharge, median (range)	1 (0-13)	1 (0-12)	0.212
Length of hospital stay of first unplanned hospitalization, median number of days (range)	6 (1-58)	6 (1-71)	0.576
Number of patients unplanned hospitalized within			
• 30 days after index discharge, n (%)	37 (19)	46 (24)	0.265
• 6 months after index discharge, n (%)	89 (46)	103 (53)	0.154
• 12 months after index discharge, n (%)	115 (60)	129 (67)	0.139
Number of patients who died within			
• 30 days after index discharge, n (%)	4 (2)	7 (4)	0.359
• 6 months after index discharge, n (%)	24 (12)	36 (19)	0.092
• 12 months after index discharge, n (%)	44 (23)	56 (29)	0.163
• 20 months after index discharge, n (%)	52 (27)	76 (39)	0.009
Number of patients who died or was unplanned hospitalized within			
• 30 days after index discharge, n (%)	41 (21)	51 (26)	0.232
• 6 months after index discharge, n (%)	96 (50)	113 (59)	0.082
• 12 months after index discharge, n (%)	125 (65)	139 (72)	0.125

DISCUSSION

Pharmacist-led medicines management in multimorbid patients did not statistically significantly prolong the time until first readmission or death compared to control patients. The result is in contrast with previous randomized controlled trials (RCTs) on similar interventions provided to other patient populations, showing a decreased readmission rate, prolonged time to readmission, and a reduction in hospital visits.[23, 40-42] This contrast may be explained by the patient population. To our knowledge, our study is the first to investigate the effect of a medicines management intervention on clinically relevant endpoints in multimorbid patients with complex drug regimens. In this population, urgent

medical care like hospital readmissions might be difficult to avoid. This theory is supported by a subgroup analysis of one of the previous RCTs, which found that in patients 80 years or older a pharmacist intervention was more effective in preventing emergency department visits in patients using less than 5 drugs compared to patients using 5 drugs or more.[28] However, it should be noted that the 95% confidence interval in our study is wide and compatible with a risk reduction of 36% as well as a 4% increased risk. The sample size calculation in the current study was based on a target 15% reduction in readmissions, which may have been optimistic, and insufficient power may therefore explain the non-significant result.

A statistically significantly increased overall survival, one of the secondary endpoints, was seen in patients in the intervention versus the control group. The hazard reduction of 34% is indisputably clinically relevant and reflects a great improvement potential in the care of multimorbid patients. To our knowledge, this is the first study to show an effect of pharmacist-led medicines management on survival. This endpoint was either not investigated[23, 42], or no effect was seen[40, 41] in the previous RCTs. The results of our study are in contrast to the recent Cochrane review concluding that “medication review does not seem to prevent death and hospital readmissions”.[22] The reason for this discrepancy is most likely multifactorial and due to differences in patient populations, characteristics of the interventions, and the duration of the follow-up. Important differences in the patient populations include older patients in the study by Gillespie et al.[40], and that the study by Ravn-Nielsen et al.[43] included patients with lower mortality than the current study, i.e. mortality rates of 10% versus 19%, respectively, in the control group at 6 months after index discharge. In our study, a thorough intervention conducted close to the patient, including medicines reconciliation both at admission and discharge as well as improved

information at discharge to ensure continuous treatment and increase adherence, may constitute characteristics of the intervention important for the effect on survival. Clinical pharmacists performing the procedures of the intervention in close collaboration with the patient, physician and other members of the treatment team are most likely also important for obtaining the effect on survival. At last, the longer follow-up in the present study, prolonged by several months compared to the other RCTs[40, 43], could have allowed prophylactic drugs added during medicine reviews enough time to achieve beneficial effects[22] and probably contributes to explain the intervention`s effect on survival.

Heterogeneity in the pharmacist-led in-hospital interventions, including various elements of various intensity, make comparisons of results amongst studies, as well as interpretation of results, challenging.[22, 44] Furthermore, such interventions are indisputably complex, and evaluating such interventions is complicated.[45, 46] The intervention consists of various components delivered as an overall intervention. With such a design, it is not known whether the overall intervention or only parts of it are important for effect. The intervention in the current study consisted of elements of the highest level of intensity, i.e. diamond level medicines reconciliation[44, 47] and advanced medicines reviews.[48] In the recent RCT from Denmark, a similar intervention of similar intensity reduced emergency department visits and hospital readmissions but did not have an effect on mortality[43], i.e. the opposite of our results. Differences in eligibility criteria, nuances in the delivered intervention and/or care delivered to control patients, clinical pharmacists` training and how they interacted with the rest of the multidisciplinary treatment team may be factors contributing to explain this. The current study nevertheless adds to the international body of literature that high-intensity, in-hospital pharmacist-led interventions to tailor drug therapy may improve clinical outcomes in high-risk patients.

The intervention had no effect on the length of stay (LOS) of the first readmission. This was not surprising, as hospitals in Norway for several years have received incentives to reduce LOS, illustrated by as short as 6 days median LOS of the first readmission in the present study. In comparison, an IMM-intervention showed a reduction from 13.1 days to 9.7 days LOS of the first readmission in Northern Ireland.[23] The number of unplanned hospitalizations during 12 months follow-up did not differ between the groups in the present study, in line with findings by Gillespie et al.[40]

Drug counts were chosen as the preferred multimorbidity measure at patient inclusion, which could be seen as a limitation. Nonetheless, this strategy resulted in the inclusion of a multimorbid patient population, as validated by diseases counts according to the generally accepted definition.[3] Our study included patients from a single hospital in Norway which may challenge the generalizability. However, the study had few exclusion criteria, thus comprising a broad population. The low drop-out rate further contributes favourably to external validity.

It was not feasible to blind participants, study pharmacists or ward physicians to group allocation. To limit bias, the study was blinded on all steps considered possible to blind. Any spill-over effect of the intervention to control patients would, in any case, reduce the effect estimate. Due to the complexity of the intervention a proportion of the intervention patients did not receive the complete intervention, which may also have contributed to the non-significance on the primary endpoint and an underestimation of the effect on survival. The broad inclusion criteria may have resulted in the inclusion of participants at low risk of readmission and death, which might also have contributed to the non-significant result on the primary endpoint, as well as buffered the effect of the intervention on survival. Studying

the effect of pharmacist-led medicines management in a subgroup of multimorbid patients at the highest risk of readmission, e.g. by stratifying on frailty, could be useful. The randomized controlled design and the long follow-up of all patients are factors that strengthen the study.

CONCLUSION

Pharmacist-led medicines management in-hospital to multimorbid patients had no statistically significant effect on time until readmission or death. A statistically significant increase in overall survival was seen. As a response to the increasing challenges of providing safe and evidence-based healthcare to high-risk multimorbid patients, further studies should be conducted to investigate the effect of such an intervention on a larger scale.

Competing interests statement

Author ML received Ph.D. funding from the South-Eastern Norway Regional Health Authority (grant number 12/00718). The other authors declare that they have no competing interests.

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Data sharing statement

The data that support the findings of this study are available from Oslo University Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Deidentified participant data are however available from the authors upon reasonable request and with permission of Oslo University Hospital, with publication. Additional related documents, e.g. patient consent forms, are available at request.

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FIGURE LEGENDS

Figure 1. Title: Graphical depiction of the study design, inspired by Perera and colleagues [29].

Objects are represented by squares and activities by circles.

Figure 2. Title: Patient flow.

Figure 3

a) Title: Time to first hospital readmission or death in the intervention versus the control group.

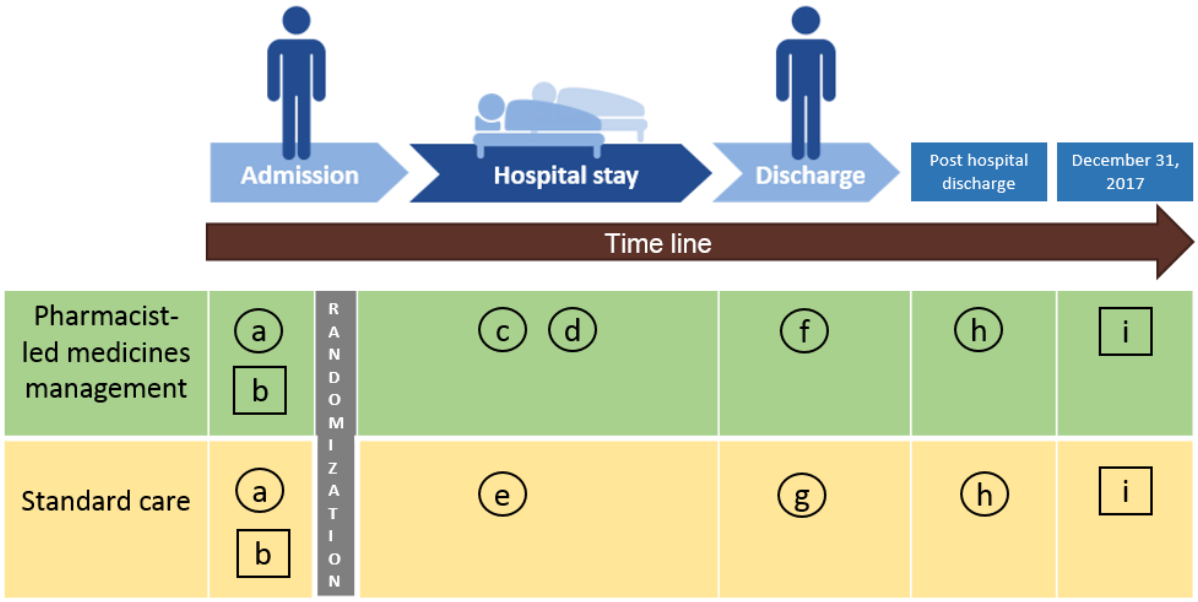
b) Title: Overall survival in the intervention versus the control group.

SUPPLEMENTARY MATERIAL

S1 Appendix. Original trial protocol, protocol amendments, statistical analysis plan, statistical analysis plan amendment and timeline of the study with milestones.

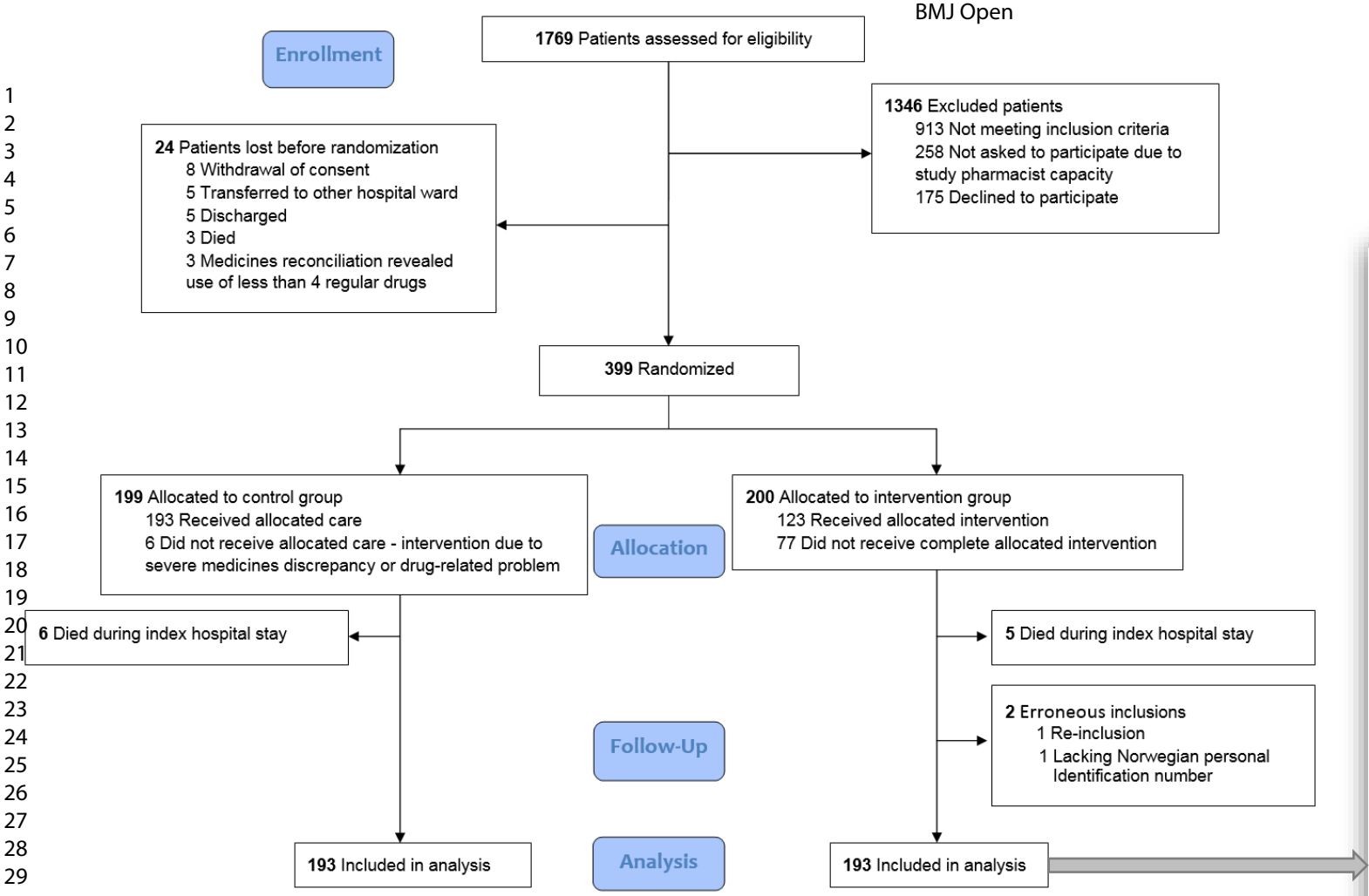
S2 Appendix. CONSORT Checklist.

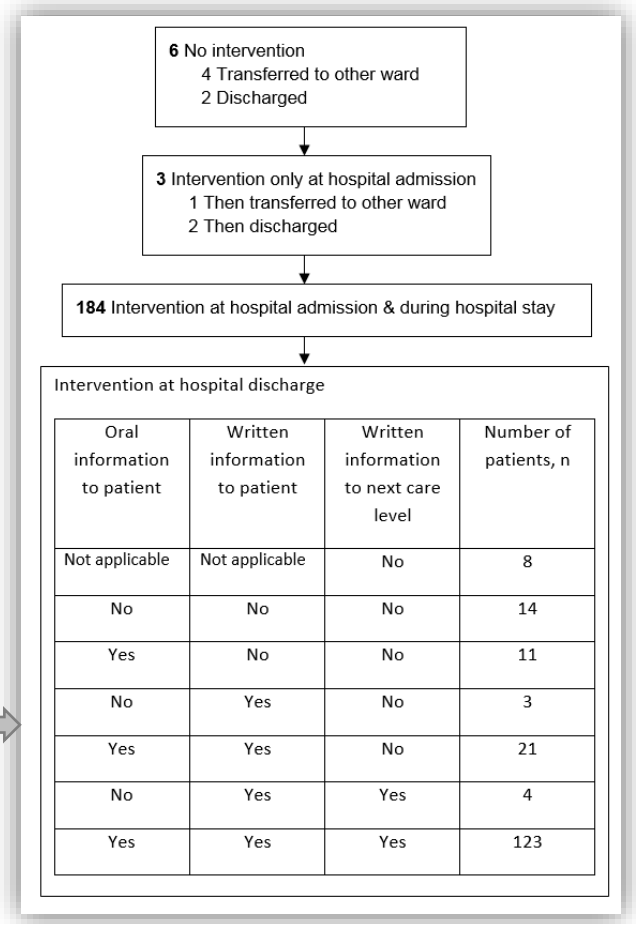
S3 Appendix. Time to first hospital readmission in the intervention versus the control group, censored for deaths.



(a)	Medicines reconciliation and review conducted by clinical pharmacist *without* discussion of medicine discrepancies or drug-related problems (DRPs) and possible solutions in the multidisciplinary team[a]
[b]	Patient characteristics collected
(c)	Multidisciplinary treatment team[a] discussions of medicine discrepancies and DRPs revealed at hospital admission and possible solutions
(d)	Medicines review conducted by clinical pharmacists by systematically addressing 11 pre-defined risk categories for each drug each patient was prescribed at a given point of time; drug monitoring, adverse effect, drug-drug interaction, non-optimal drug therapy, reduced organ function/contraindication, inappropriate drug in elderly, unnecessary drug, course length, practical problem, adherence issue and other. Medicines reviews were performed at admission and repeatedly as needed due to changes in either prescription, patient symptoms, clinical state, and/or laboratory values. Patients were reviewed for such changes daily, Monday to Friday, during regular daytime working hours. Consecutively multidisciplinary treatment team[a] discussions of identified DRPs and possible solutions.
(e)	Standard in-hospital care provided by physicians with internal medicine expertize, nursing staff and when needed; clinical nutrition physiologists and/or physiotherapists
(f)	Medicines reconciliation, followed by written and verbal information tailored to the patient`s further needs of care, as well as discharge activities aiming to ensure continuous treatment and increase adherence: • Written systematic information comprising a reconciled drug list with description and justification for all changes made during the hospital stay, to the next care provider[b] (all patients), and to the patient/relative if they to some extent would be involved in handling the drugs after discharge • Verbal information/conversation with the patient and/or relative adapted to the patient needs[c] - if they to some extent would be involved in handling the drugs after discharge • Assistance with retrieving drugs from the pharmacy, if needed • Providing the patient with drugs from the hospital pending on an updated multidose delivery, if needed
(g)	Discharge medicine information (not standardized) provided by physicians with internal medicine expertize and nursing staff
(h)	Standard care in the primary health care (details not collected)
[i]	Last day of follow-up on readmissions and mortality outcomes

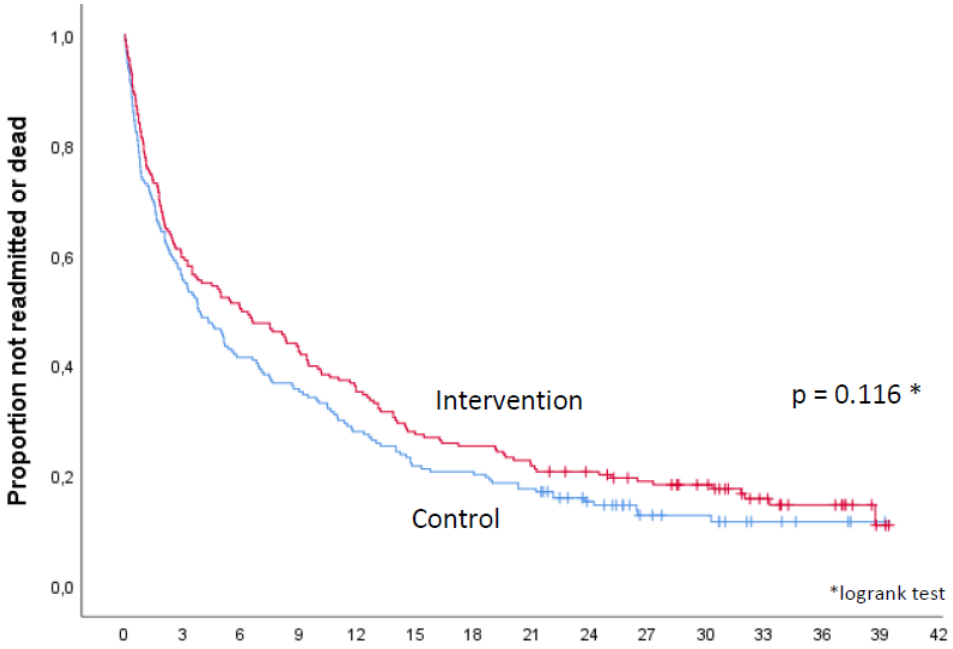
[a] The multidisciplinary treatment team consisted of physician with expertise in internal medicine, nursing staff, clinical pharmacist, and when needed; clinical nutrition physiologists and/or physiotherapists
[b] The general practitioner, nursing home, home nurse and/or multidose delivering pharmacy.
[c] Sometimes regarding the entire drug list, sometimes the most important changes, sometimes regarding one specific drug. If the patient was considered to benefit from any provided information or given the opportunity to ask questions, such a targeted conversation was conducted, even if a complex conversation was not considered favorable.





Oral information to patient	Written information to patient	Written information to next care level	Number of patients, n
Not applicable	Not applicable	No	8
No	No	No	14
Yes	No	No	11
No	Yes	No	3
Yes	Yes	No	21
No	Yes	Yes	4
Yes	Yes	Yes	123

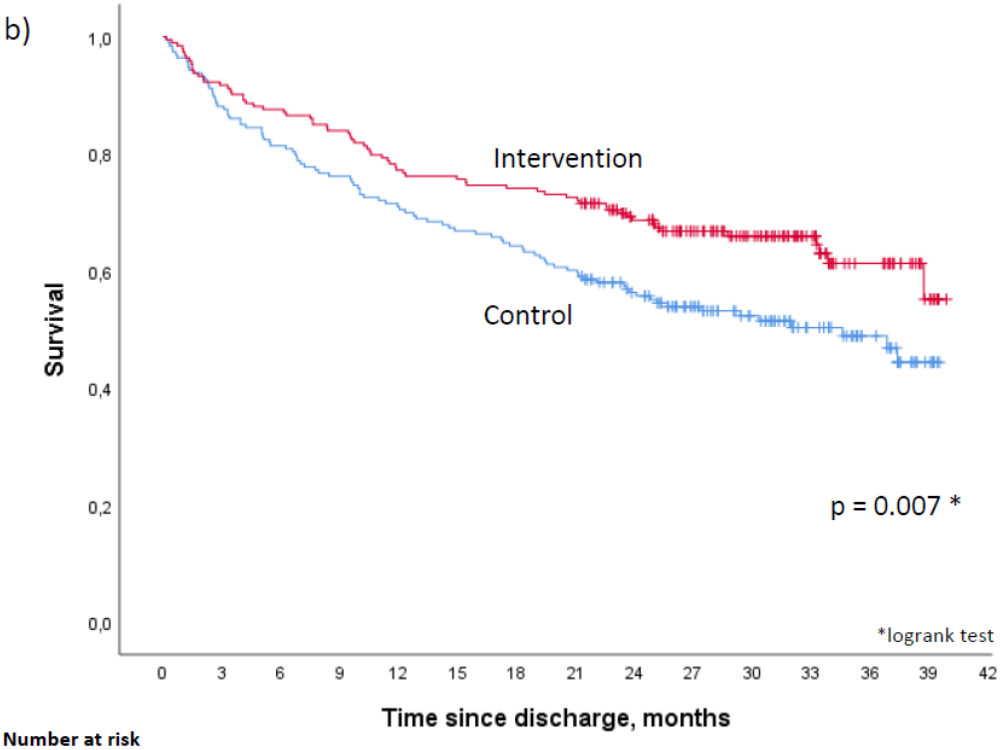
a)



Number at risk

Intervention	193	115	97	82	68	53	49	42	37	31	26	15	10	2
Control	193	107	80	69	54	42	40	34	23	13	11	5	3	1

b)



Number at risk

Intervention	193	177	169	162	149	146	143	140	115	93	73	49	27	8
Control	193	170	157	147	137	129	124	116	97	76	59	40	25	7

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

Project leader and co-supervisor: Associate professor at University of Oslo, Norway, Head of the internal medicine ward at Oslo University Hospital, Norway, MD, PhD Morten Mowe, mormow@ous-hf.no

PhD student and responsible study pharmacist: Marianne Lea, MScPharm, MScClinPharm, marianne.lea@sykehusapotekene.no

Responsible for the study: Oslo University Hospital, Norway. Contact: Morten Mowe, head of the internal medicine ward, mormow@ous-hf.no

Responsible for data processing: Oslo University Hospital, Norway. Contact: Morten Mowe, head of the internal medicine ward, mormow@ous-hf.no

Other project members and collaborators:

- Espen Molden, professor at the School of Pharmacy, University of Oslo, Norway main supervisor
- Liv Mathiesen, Dr. scient, head of research and development, Hospital Pharmacies Enterprise, co-supervisor
- Kristin Hestad, section head nurse of the internal medicine ward, The Medical Clinic, Oslo University Hospital, project member
- Anne Mette Njaastad, senior physician at the internal medicine ward , The Medical Clinic, Oslo University Hospital, project member
- Kristin Thomassen, quality adviser, The Medical Clinic Oslo University Hospital, project member
- Britt Petterson, nurse at the internal medicine ward , The Medical Clinic, Oslo University Hospital, project member
- Anette Engnes, master student at the School of Pharmacy, University of Oslo, Norway, project member

Torhild Heggestad, MD, PhD, advisor in Helse-Bergen, Norway, collaborator

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.

Contents

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

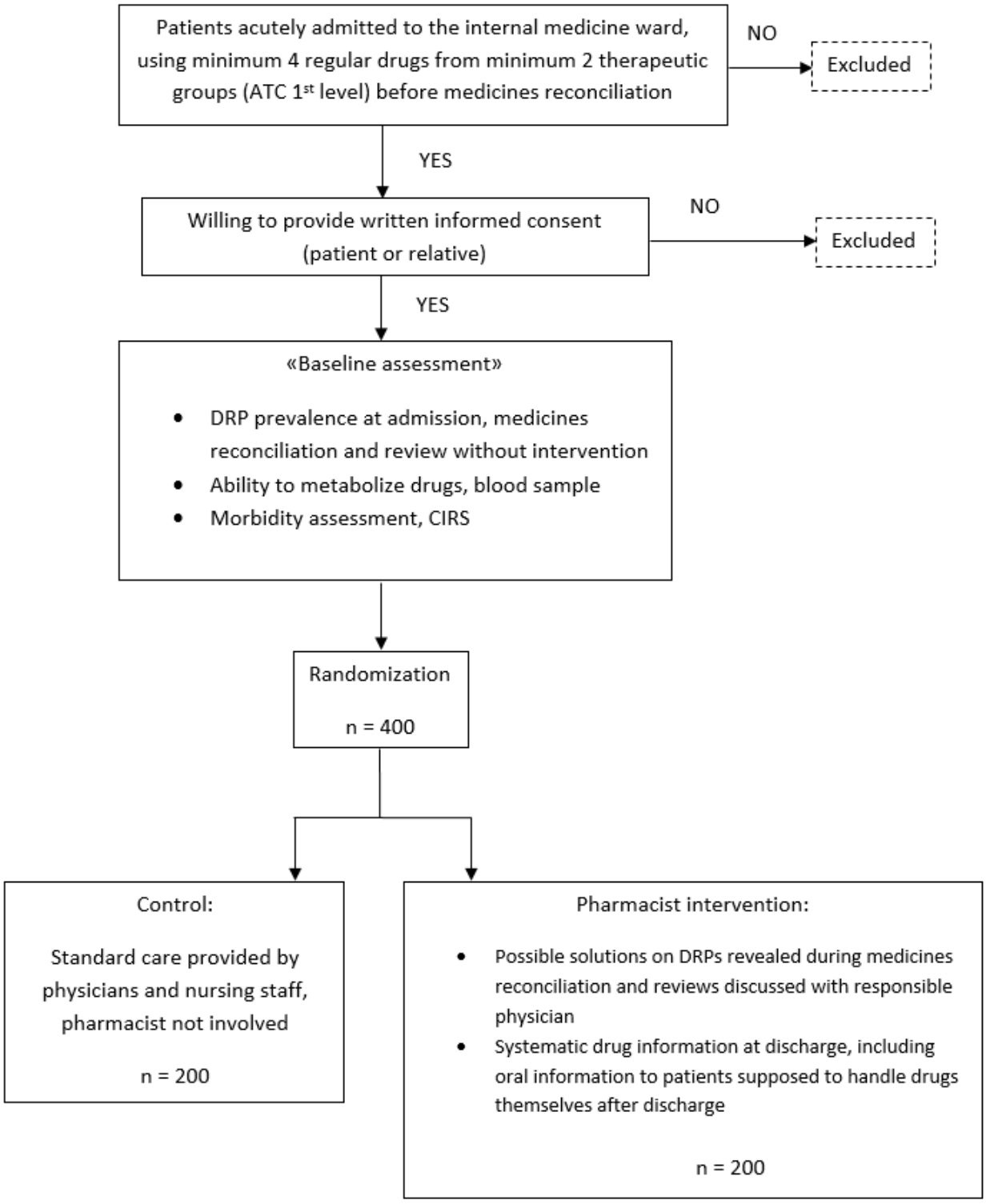


Figure 1. Overview over how the study will be conducted.
ATC = Anatomical Therapeutic Chemical, DRP = drug-related problems, CIRS = Cumulative Illness Rating Scale.

”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.

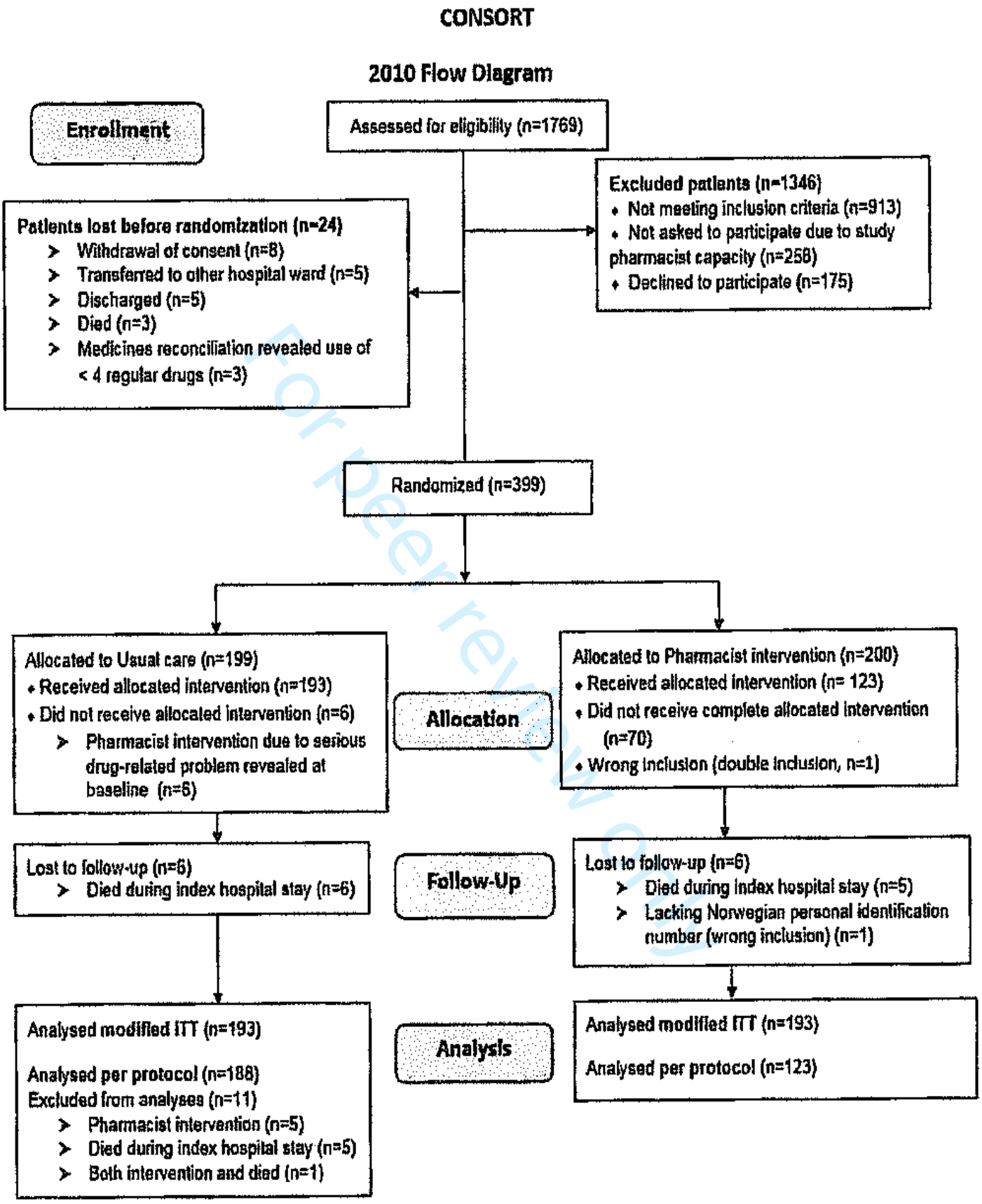
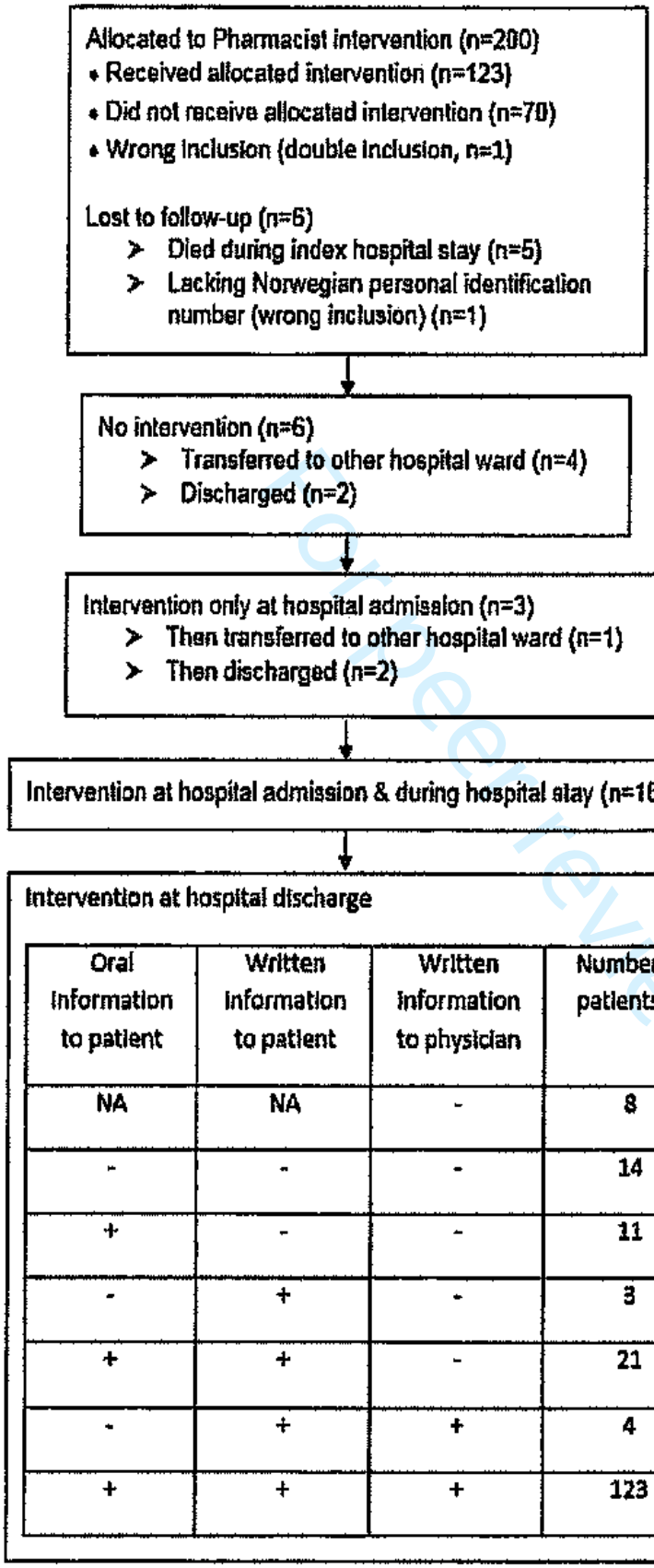


Figure 1. Patient flowchart. ITT = intention to treat.



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
Main supervisor
University of Oslo

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.

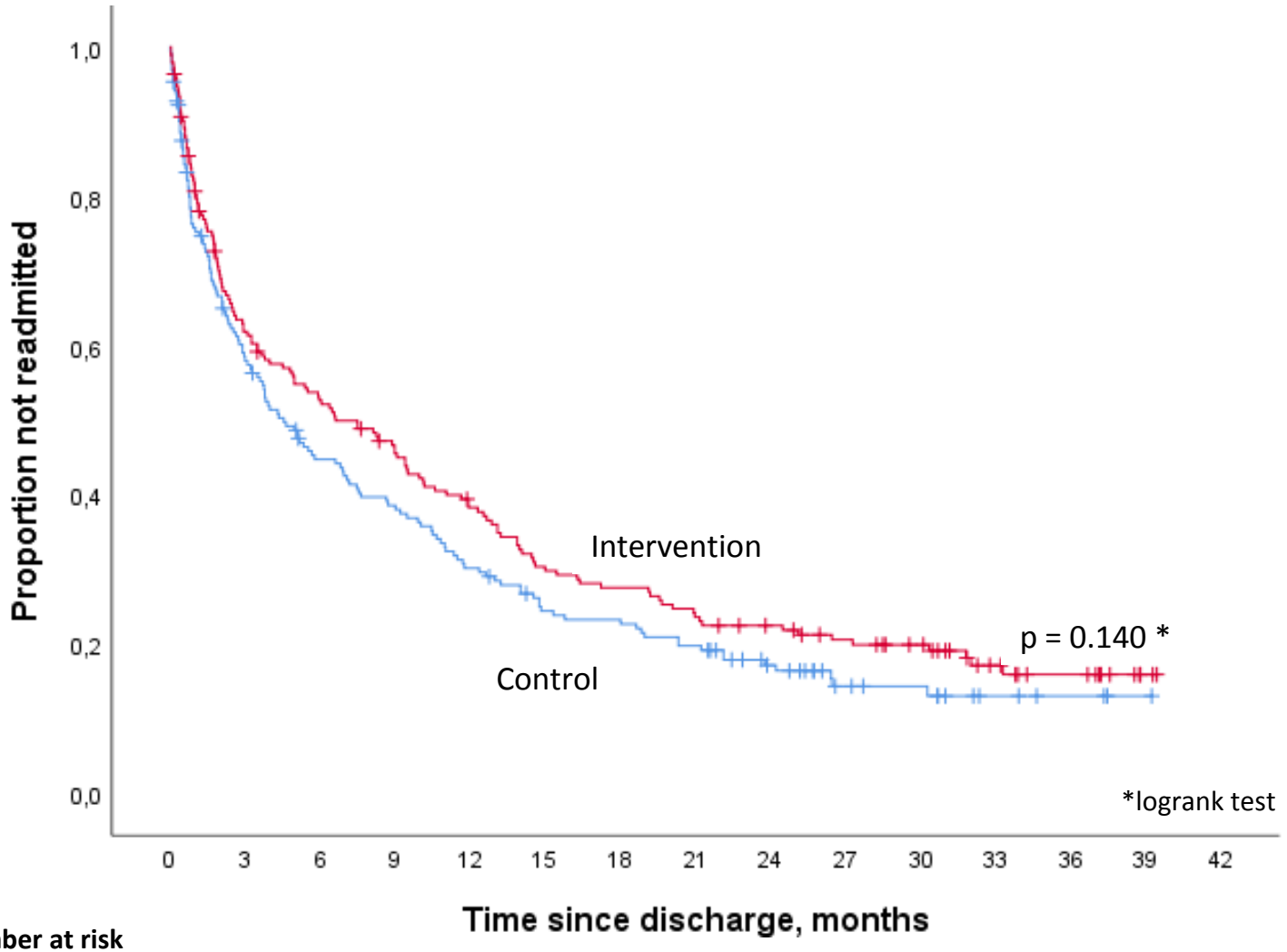
**Huge workload at the Registers entails a very long processing time for outcome data.

CONSORT CHECKLIST

Table. CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial[a]

Section and Topic	Item No.	Checklist Item	Reported on Page No.
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Comment			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

[a]We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.



Number at risk

Intervention	193	115	97	82	68	53	49	42	37	31	26	15	10	2
Control	193	107	80	69	54	42	40	34	23	13	11	5	3	1