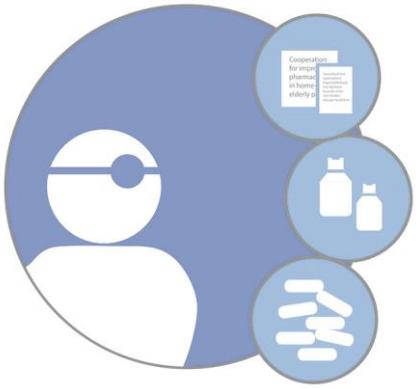
Cooperation for improved pharmacotherapy in home-dwelling elderly people receiving polypharmacy

The COOP Study

A cluster randomized controlled trial



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1. Background

Polypharmacy is frequent among elderly people (1), and the consumption of drugs in this group have increased in the last decades (2). In 2008, persons aged 70+ constituted 15 % of all drug users in Norway, but received 35 % of all prescriptions (3). It has recently been shown that 20 % of Norwegians aged 70+ are prescribed more than ten different drugs annually (4), and in addition comes the consumption of over-the-counter drugs and herbal remedies. In a study of drug consumption among users of home services aged above 65 years in eight European countries (including Norway), 51 % of the participants used more than six different drugs and 22 % used more than nine different drugs during a week (5). The use of drugs is even more extensive in Norwegian nursing homes (6, 7), and the most frail of the home-dwelling elderly can be presumed to have a consumption similar to that of the nursing home patients.

A complex clinical situation may necessitate a high number of drugs, and a properly titrated polypharmacy may be beneficial for the individual patient. However, most clinical guidelines are targeted for less complex situations and based upon research carried out in patients with a limited number of co-morbid conditions. Accordingly, such guidelines may be of limited validity in frail and multi-morbid elderly patients (8, 9). The more drugs an individual patient consumes, the more demanding is the trade-off between benefit and harm, and the more tightly should the clinical condition be monitored. Polypharmacy increases the risk of adverse drug effects, interactions and other drug-related problems, and the risk seems to increase almost linearly with the number of drugs (10-12). The risk of poor compliance will naturally also increase with more complex drug regimens (13). Several Norwegian and international studies indicate that inappropriate drug use is a major reason for poor health and impaired function in the elderly (14-16) as well as for potentially avoidable hospital admissions (17-19), and also may be lethal (20). It has been estimated that one in four patients admitted to hospital are prescribed at least one inappropriate medication and that up to 20 % of all inpatient deaths are attributed to potentially preventable adverse drug reactions (21). Such clinical problems are often caused by over-medication, the choice of inappropriate drugs or inadequate monitoring and follow-up (14). Under-use of potentially beneficial drugs is also a significant problem (22, 23).

Optimization of pharmacotherapy must be based on a comprehensive assessment of all relevant medical conditions as well as the patient's functional ability, resources and preferences. Health services are organised in a way that makes it difficult to attain a sufficiently good view of the clinical situation in order to make a good drug review in frail and multi-morbid patients. Specialists in hospital will naturally focus upon drugs that are relevant for the organ system in which they have specialized. General practitioners, on the other side, attain limited experience in handling such complex health states, and will naturally be reluctant to change medication that was in many instances initiated by a hospital specialist (24). Geriatricians are trained in the management of complex health conditions and polypharmacy and have firm knowledge of age-related changes in physiology and pharmacology (25), but typically see patients over a limited period of time, either in an acute geriatric ward or in the geriatric out-patient department. Thus, the geriatrician often has limited knowledge about the patient's medical history and has a limited possibility to follow the patient over time, elements that are typical strengths in the follow-up made by the family physician. Geriatricians and family physicians therefore have complementary strengths for managing complex drug regimens in frail elderly patients, and a closer and more structured cooperation between these two specialities could be hypothesised to be beneficial for home-dwelling, frail elderly patients using multiple medications. The limited amount of research that has been carried out in this field also seems to indicate that one of the most effective interventions is multidisciplinary case conferences involving a geriatrician (26, 27).

Optimal drug treatment for frail, home-dwelling elderly necessitates a streamlined cooperation between several professionals and services, the hospitals mainly seeing the patients during acute exacerbations of their chronic diseases, the family physicians being responsible for prescriptions most of the time, and the home nursing service being in the best position for monitoring compliance, effect and adverse reactions. Suboptimal drug use may result in impaired function, thus putting more strain on the home nursing service and the close relatives, and may also lead to an increased need for nursing home beds. The cooperation between hospitals and primary health care in Norway has been reorganised through "The Interaction Reform" ("Samhandlingsreformen"), emphasising closer cooperation and competence exchange between hospital doctors and family physicians (28). Safer drug use among the elderly is also emphasised through the Patient Safety Campaign initiated by the Ministry of Health. Drug reviews are now firmly recommended for nursing home patients, and is recently suggested to be mandatory for patients on the family physicians' lists using more than six drugs regularly. There is, however, a severe lack of scientifically based evaluations of specific measures designed to attain the goals of such politically driven reforms.

A majority of interventions for improvement of drug treatment in the elderly are evaluated by the use of surrogate outcomes such as drug-related problems (29), number of prescribed drugs (30) or prevalence of potentially inappropriate prescriptions (31). Many studies also suffer from a sub-optimal design, such as observational studies and interventional studies without a control group (26) or without randomization (32). A recent Cochrane review (33) concluded that interventions to improve appropriate polypharmacy appear beneficial in terms of reducing inappropriate prescribing, but that it is unclear whether they result in a clinically significant improvement. This review firmly recommends that future studies should focus upon clinical outcomes (33). Interventional studies of measures to facilitate better prescriptions, using a scientifically sound design and at the same time utilizing patient-relevant end-points as well as end-points capturing the effect upon the families, the municipal services and the cooperation between them and with the specialist health care services, are so far very rare.

2. Aim

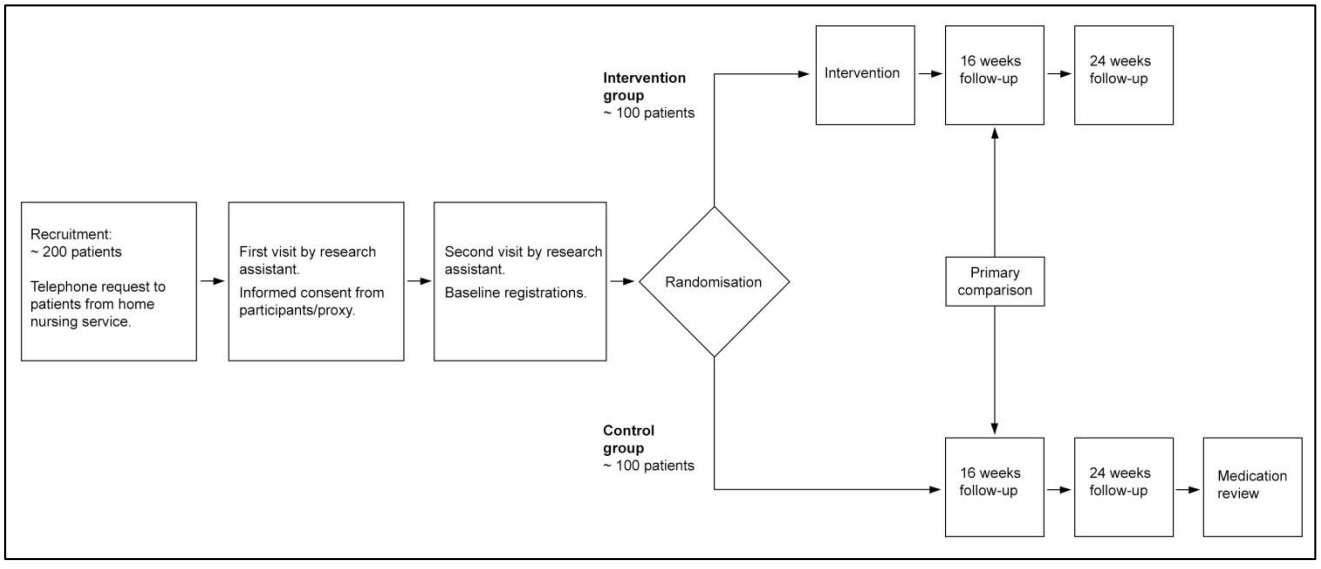
The primary objective of this project is to evaluate the effect upon patients, relatives and local health care service of a structured cooperation between a hospital-based geriatrician and family physicians on complex drug regimens in home-dwelling frail elderly patients. Secondary objectives are to study other aspects of drug use, e.g. the medication changes proposed by the described cooperation, the prescription appropriateness in this patient group, to evaluate the use of pharmacogenetic tests as a tool for optimized treatment, and to examine adverse drug reactions and adverse drug withdrawal events in the intervention group.

3. Design

This is a 24 weeks cluster randomized, single-blinded, controlled trial. We will carry out cluster randomization on physician level instead of individual randomization on patient level, in order to avoid "contamination" of the control group by ideas provided by the geriatrician for patients in the intervention group.

We will assess the outcomes at 16 and 24 weeks, counted from baseline, and will also assess baseline values for the outcomes in order to adjust for potential inequalities. Patient flow in the RCT is illustrated in the figure. Randomization will be computer generated and carried out in blocks of unknown and variable size. In order to minimize the risk of selection bias, randomization will take place after inclusion of all patients within each cluster. To assure as equal group sizes as possible, we will also stratify the family physicians based on the number of patients on their lists taking part in the study; 1-2 patients versus 3 or more. The family physicians will be included sequentially according to the capacity in the project, thus making it possible to keep the research assistant blinded with respect to allocation.

We suppose that such a comprehensive clinical evaluation and drug review that we will test, is most relevant for patients with relatively pronounced polypharmacy. It has previously been shown that conventionally used limits for "polypharmacy", e.g. five drugs used regularly, identifies many patients without particular complex health states and without drug related problems (11). We will therefore limit this project to patients using seven regular drugs or more, in order to increase the likelihood that they may benefit from a drug review.



4. Intervention

Successful interventions for geriatric patients have often been of a complex type (34-36), whereas the implementation of one single measure will be less likely to give an effect. A major challenge when studying complex interventions is to describe the intervention with sufficient precision as to facilitate replication (34). Our main strategy for this will be to compensate for the necessary degree of pragmatism in the interventional approach with a detailed description of the interventions that were in fact carried out, in particular changes in the drug regimens of the individual patients.

Our intervention will constitute of three main parts: geriatric assessment of the patient and medication; a targeted conference between the geriatrician and the family physician; and a pragmatic follow-up by the two physicians in cooperation.

a. Geriatric assessment

The patients will be seen by a physician trained in geriatric medicine (the PhD student in this project). This visit may occur in the patient's own home or at the hospital's out-patient geriatric department, depending on what is considered as appropriate in each case. In beforehand, the project physician will provide necessary facts on the patient's medical history and actual medication from the hospital records, the family physician, the home nursing service, and other relevant sources. The physician will carry out a medical history from the patient (if necessary supplemented by a close relative, for example if the patient has dementia or severe depression) and a physical examination, both with focus on conditions most relevant for the patient's total medication. Relevant blood analyses and other supplementary test will be ordered if not already available (ECG, haematological tests, electrolytes, renal function, natriuretic peptides, thyroid function, nutritional indicators, serum concentration of relevant drugs, pharmacogenetic testing etc.). The geriatric work-up will be aimed at evaluating whether current medications are indicated, whether the relevant conditions are satisfactorily compensated, whether the dosages are appropriate, whether the patient has symptoms that may in reality be adverse drug effects, and whether drug-drug interactions or drug-disease interactions are likely to occur. The project physician will use published tools like the STOPP/START criteria (37) and the NORGEP criteria (38) as appropriate in each particular case. The project physician will also be provided with clinical supervision from a consultant in geriatric medicine.

b. Conference with common drug review

This is an essential part of our intervention, and will normally take place at the family physician's office. Other places or a telephone conference can be used if convenient. The main purpose of this conference is to combine the competence of the geriatrician and that of the family physician in a focused drug review. The two physicians will discuss the patient's drug list systematically. The geriatrician may suggest changes in the drug regimen, but the family physician retains the medical responsibility for the patient and is in charge of all ordinations and medication changes.

c. Clinical follow-up

Depending on medication changes that have been done, the two physicians will arrange the necessary follow-up within the project period. The follow-up can consist of a clinical evaluation, further drug adjustments, blood tests etc., and can be carried out by the geriatrician, the family physician, or through telephone contact with the patient, the relative or the home nursing service, depending on the circumstances.

5. Inclusion criteria

- The patients must be on the list of one of the family physicians participating in the study
- Home dwelling (not permanently institutionalised)
- Medications administered by the home nursing service
- Age 70 years or more
- Polypharmacy defined as the use of at least seven different systemic medications taken regularly (drugs taken weekly, e.g. alendronate, are included, but not topical drugs like eye drops and ointments)
- Informed consent by the patient or a close relative (if the patient is unable to give a valid informed consent, see also section 13)

6. Exclusion criteria

- Patient or relative denies inclusion
- The family physician does not want the particular patient to participate
- Moderate/severe dementia (Clinical Dementia Rating Scale score > 1) and contact with the closest proxy less than once every other week.
- The patient does not speak/understand Norwegian.
- Expected to become permanently institutionalised within 24 weeks
- Life expectancy six months or less (e.g. disseminated cancer, advanced heart failure, respiratory failure or renal failure)

7. Methods

Family physicians from the municipalities in the northern part of Akershus county and southern part of Oppland county, Norway, will be invited to participate in the project with patients from their lists. All family physicians in these areas are eligible, and they can choose to participate with 1-5 patients each. If necessary, in order to include the planned number of patients, the geographic area for recruitment can be expanded to other parts of these counties and/or Oslo.

We will then cooperate with the home nursing service in each municipality to identify the patients. An employee from the home nursing service will screen their patient registry and identify patients that are both on the participating physician's lists and meet the other inclusion criteria. The family physician will review this list and consider if any of the exclusion criteria are present. If there are more eligible patients than the physician wants to participate with, he/she decides which of the patients to ask for participation. The patients (or a family member) will have a phone call from the home nursing service, explaining the study and asking for an oral consent. If this is achieved, the patients will be seen in their home by a research assistant, who will give complementary information orally and written and obtain a written consent (if the patients are still interested). This procedure will ensure that the patient's identity remains undisclosed to the researchers until they have consented to participate.

Two pilot studies have been carried out, in 2011 and 2013. In these studies, we tried out two different approaches where the family physicians were asked to identify relevant patients for the project themselves. Both studies indicated that this was difficult, mostly due to time pressure, even if the physicians were highly motivated. Based on these experiences, we have planned to identify the patients with help from the home nursing service, as described above. If the home nursing service in a certain municipality does not wish to participate, the family physicians are allowed to identify patients themselves. In such cases, the family physicians must screen their lists over patients having medications administered by the home nursing service, and ask eligible patients if they accept a visit from our research assistant (as described above).

8. Outcome measures

a. Primary endpoint

As primary endpoint we will use 15D, measured 16 weeks after the intervention. 15D is a questionnaire concerning different aspects of health-related quality of life (HRQoL) (39) that has been used in similar geriatric interventions (40, 41). It is a generic 15-dimensional measure that has been validated systematically internationally in various populations and patient samples (42). The 15D instrument may be used not only as a profile measure, but also as a single index. The index varies between 0 (poorest HRQoL) and 1 (excellent HRQoL). Dimensions of the 15D are mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. Usually the 15D questionnaire is filled in by the individual whom it concerns, but it may also be administered in an interview with the participant or his/her proxy.

We hypothesise that most improvements in the total drug regimen of frail elderly patients, being it better pain control, better symptom control in heart failure or COPD, less parkinsonian side effects, less iatrogenic dehydration, less sedation etc., will have the potential to improve HRQoL. Accordingly, in our opinion 15D is an appropriate outcome measure when the aim is to improve the total drug regimen in an individualised manner across a broad spectrum of drug classes. The patients included in our study will be old, and many may not be familiar with self-administration of questionnaires of this kind. We will therefore administer 15D by interview. This will be done by the research assistant, blind to group allocation. If the patient has a moderate or severe dementia (Clinical Dementia Rating Scale > 1), and/or the research assistant consider that they don't

understand the questionnaire, the interview will be carried out with the closest proxy. To account for patients that might loose their ability to respond to 15D during the follow-up period, and in order to possibly compare the answers given by patients themselves and their proxies, we plan to administer 15D to the closest proxy in all cases where possible.

b. Secondary endpoints
Secondary endpoints will be on the patient, family and local community level. Follow-up will occur at 16 and 24 weeks after baseline registrations, in order to study the course of any improvement over time.

i. Patient related endpoints
- 15D after 24 weeks
- Short Physical Performance Battery (SPPB), a simple test of mobility that combines the results of walking speed, chair stand and balance tests (43)
- Gait speed (44)
- Hand grip strength (hand dynamometry)
- Functional Independence Measure (FIM), a measure of physical and cognitive disability (45)
- Trail Making Test A and B, measuring processing speed, focused and split attention, and executive functioning (46)
- "Digit Span", a digit repetition test of working memory measuring attention (47)
- Five Digits Test, measuring attention and executive functions (48)
- Appropriateness of current prescribing as assessed by the Medication Appropriateness Index (MAI) (49) and the Assessment of Underutilization (AOU) (50), as assessed by a clinical pharmacist and/or a consultant in geriatric medicine not otherwise involved in the intervention
- Number of falls, recorded with the aid of diaries kept by patients/caregivers
- Orthostatic blood pressure
- Weight
- Mortality

ii. Family related endpoint
- Carer burden according to the Relative Stress Scale (RSS) (51), a scale with high acceptability an with which we have good experience from prior research on elderly patients with a variety of chronic conditions (52, 53).

iii. Endpoints related to local community and family physician
- Hospital admissions (with reasons) during the first 24 weeks after baseline
- Number of days the patient has spent in his or her own home (in contrast to being in hospital or nursing home) during the first 24 weeks after baseline
- Admission to permanent institutional care, during the first 24 weeks after baseline
- Current use of home nursing service (hours per week) during the first 24 weeks after baseline
- All changes in the pharmacotherapy taking place during the intervention and the clinical follow-up period (24 weeks), and reasons for any non-compliance (from the patient, the family physician or the home nursing service) with the advice given by the geriatrician

9. Baseline measurements
The outcome measures will also be measured at baseline (before the intervention), in order to check and adjust for possible inequalities. In addition, the following descriptive variables will be registered:
- Demographic data
- Diagnoses according to ICD-10
- Cumulative Illness Rating Score (CIRS) (54)
- Clinical Dementia Rating Scale (CDR) (55)
- Course of cognitive symptoms during the last ten years, according to the validated and commonly used proxy scale Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (56)
- Nutritional status, assessed by the Mini Nutritional Assessment Short Form (MNA-SF)(57)
- Current drug use

Table 1. Study assessment procedures and timetable

	Baseline visit	16 weeks follow-up	24 weeks follow-up
Assessments directly involving the patients			
Descriptive variables (demographics, diagnoses, CIRS, MNA-SF)	x		
15D	x	x	x
SPPB + gait speed	x	x	x
Hand grip strength	x	x	x
Trail making test A + B	x	x	x
Five Digits Test	x	x	x
Digit Span	x	x	x
Falls (filled out with help from caregivers if necessary)		x	x
Orthostatic blood pressure	x	x	x
Weight	x	x	x
Assessments of drug use			
Current drug use and changes in pharmacotherapy	x	x	x
MAI	x	x	x
AOU	x	x	x
Assessments based on observation, information from a close relative and/or the home nursing service			
FIM	x	x	x
CDR	x		
Assessments based on information from a close relative			
15D	x	x	x
RSS	x	x	x
IQCODE	x		
Administrative data			
Hospital admissions (with reasons)		x	x
Number of days in own home		x	x
Admission to permanent institutional care		x	x
Use of home nursing service (hours per week)	x	x	x
Mortality		x	x

10. Statistics, power, and number of participants

The primary endpoint 15D is on an interval scale, and is expected to be reasonably normally distributed. We will analyse this measure by ANCOVA, as recommended by Vickers & Altman (58), thus taking into account the baseline values as well as the clusters (as we expect that patients recruited from the same family physician will not be completely independent). Other outcome measures will be analysed by ANCOVA (continuous data) or logistic regression (categorical data) as appropriate. Non-normally distributed variables will be transformed in order to try to achieve a distribution that is more feasible for analysis. The effects of the intervention will be analysed blindly, i.e. with the two randomisation groups denominated "A" and "B" but without knowledge regarding which group is the control and the intervention group, respectively. A detailed Statistical Analysis Plan (SAP) will be developed that will detail imputation processes for missing data etc.

The number of patients in the intervention group is planned to be 100. In order to avoid large variation in cluster sizes, we have decided that each family physician can participate with 1-5 patients. This means that the number of physicians (clusters) will be 20-100 in the intervention group. A similar number of patients and physicians will be included in the control group. To assure as equal group sizes as possible, we will also stratify the family physicians based on the number of patients on their lists taking part in the study (1-2 patients vs 3 patients or more).

It is difficult to make valid assumptions on the correlation between patients within each cluster (physician). In order to estimate the power of the study, we have chosen to estimate power in a worst case (perfect correlation) and a best case (no correlation) scenario. The true correlation is expected to be much closer to the latter, as the potential for intervention will vary between the individual patients. Based on previous studies using 15D, the standard deviation of change over time is expected to be between 0.07 and 0.08 (40, 41, 59). The minimum important change (MIC) for the change in 15D scores is +/- 0.015. A change of > 0.035 represent “much worse”, and a change of < -0.035 ”much better” (60). Based on previous studies, in addition to a pilot study, we believe that our intervention is extensive enough to potentially improve the patients HRQOL to “much

better" (<-0.035) (40, 41). As can be seen from the table below, the power to detect a difference of 0.035 will be in the range 59 to 94%, and most probably >80%.

Table 2. Estimation of power in different scenarios

Δ	SD	r	Power %
0.035	0.08	1	59
0.035	0.08	0	87
0.035	0.07	1	71
0.035	0.07	0	94
0.025	0.07	1	43
0.025	0.07	0	71

Δ = Change in 15D score.
SD = Standard deviation of change over time in 15D score.
r = Correlation between patients within each cluster (1 = perfect correlation, 0 = no correlation).

11. Publication plan

The result of the project, being it positive, negative or neutral, will be published in peer-reviewed scientific journals. The PhD-student will act as the first author and the project leader as the last author. Other members of the project group will act as co-authors according to the Vancouver criteria. We plan the following publications for the PhD-student:

1. Results of the RCT (primary and secondary endpoints supplemented by before - after - analyses).
2. Relationship between pharmacogenetics and adverse events in the first 100 patients in the material.
3. Detailed analysis of the advices given by the geriatrician, the degree of compliance with the advices, and the reasons for non-compliance.

12. Milestones

- 2nd quarter 2013 – 4th quarter 2013. Detailed planning of the study. Piloting.
- 2014: PhD student on maternity leave.
- 1st quarter 2015 – 4th quarter 2016. Inclusion of patients. Intervention.
- 2nd quarter 2015 – 4th quarter 2015. Analysis and writing of paper 1.
- 1st quarter 2016 – 3rd quarter 2016. Analysis and writing of paper 2.
- 2nd quarter 2016 – 4th quarter 2016. Construction, proof-reading and quality control of database (in parallel with continuous recruitment and intervention. Drafting of papers 3-4 (while awaiting the database to be complete and final analyses to be made).
- 1st quarter 2017 - 2nd quarter 2018. Analysis and writing of papers 3-4.

13. Ethics and formalities

The project has been discussed by the Regional Committee for Medical and Health Research Ethics (REK) on the 19th of September 2014. REK considers the purpose of the project to be to investigate factors related to the health-care system, and not to generate new knowledge about drug treatment *per se*. The study is therefore exempt from review in Norway, and can be implemented without the approval by the Regional Committee for Medical and Health Research Ethics. We will apply for consent for the project from the Data Protection Authorities. Research data will be stored at the data server dedicated for research at Oslo University Hospital.

The participating family physicians will be given comprehensive information about the project, and must consent to participate and give permission to the use of patients from their list. Inclusion of patients in the project will be based upon informed consent, and information will be given written as well as orally (see also section 7). Patient anonymity towards the researchers will be secured until the patient has consented to participation. Some patients who otherwise fulfil the inclusion criteria may be unable to give a valid consent due to dementia. We regard such patients to be particularly vulnerable to suboptimal pharmacotherapy, and thus particularly important to include in this project. We will therefore include such patients based on informed consent from a close relative in combination with assent from the patient. If the patients are able to understand basic information about the project, we will use a simplified consent form in combination with fully informed consent from a close relative.

We consider the risk upon the patients to be minimal in the project, as the intervention consists of a presumably more thorough and more competent drug review than what would else be performed. Still, we can not rule out that the patients might experience for instance adverse drug reactions if new drugs are added, or adverse withdrawal events if drugs are discontinuated. The control group will receive "usual care" from their family physician during the study period. Since we believe it is more likely that the intervention will be beneficial than harmful, it might be ethically dubious to randomise a group of patients to be assessed, but else receive no intervention. Accordingly, we plan to offer the family physicians our assistance in performing a medication review in the control group after the study period is completed.

We plan to use pharmacogenetic tests as a tool for optimalization of drug therapy. These tests are widely available for clinical use, and give information on genetic variations in metabolic pathways which can affect individual responses to drugs. We will not do analyzes with respect to genetic disorders.

14. Project group

- Professor Torgeir Bruun Wyller, Department of Geriatric Medicine, Oslo University Hospital. Project leader (geriatrics)
- Dr. Rita Romskaug, Department of Geriatric Medicine, University of Oslo. PhD student
- Professor Jørund Straand, Department of General Practice, University of Oslo (general practice)
- Professor Espen Molden, Institute of Pharmacy, University of Oslo (pharmacy)
- Professor Anette Hylen Ranhoff, Kavli's Research Centre for Ageing and Dementia and the University of Bergen (geriatrics)
- Professor Knut Engedal, Norwegian Centre for Research, Education and Service Development within Ageing and Health (old age psychiatry, cognitive assessment)
- PhD Hege Kersten, Norwegian Centre for Research, Education and Service Development within Ageing and Health (pharmacy)
- Professor Christofer Lundqvist, Research Centre, Akershus University Hospital (neurology, neurochemistry)
- Professor Eva Skovlund, Insitute of Pharmacy, University of Oslo (statistician)
- Professor Kaisu Pitkala, University of Helsinki, Finland (geriatrics, drug use in the elderly).
- Head of Service/Senior Lecturer Simon P. Conroy, Geriatric Medicine, University Hospitals of Leicester/University of Leicester, UK (geriatrics, research on complex interventions)

15. Literature

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