Statistical analysis plan

THE COOP STUDY

Cooperation between geriatricians and general practitioners for improved pharmacotherapy in home-dwelling elderly people receiving polypharmacy

1. Introduction

Polypharmacy and inappropriate drug use is associated with negative health outcomes among older people. The main objective of this study is to evaluate the effect upon patient relevant endpoints of a cooperation between geriatricians and general practitioners on complex drug regimens in home-dwelling elderly people. The detailed study protocol has been published [1], and the study is registered in ClinicalTrials.gov (NCT02379455). Some basic elements from the protocol are recapitulated below. The aim of this document is: 1) to review key elements from the protocol in light of what we know now that recruitment is completed and all assessments carried out; 2) prior to any unblinding of data, to establish details of the statistical analysis that were not finalised when the protocol was published.

Patient inclusion criteria

- Listed with one of the participating GPs
- Home-dwelling
- Medications administered by the home nursing service
- Age 70 years or more
- Use of at least seven different systemic medications taken regularly (preparations for inhalation, vitamin supplements and laxatives are included, but not topical drugs like eye drops and ointments)
- Signed informed consent given by the patient or his/her closest proxy

Patient exclusion criteria

- Expected to become permanently institutionalised within six months
- Life expectancy judged to be six months or less
- Moderate/severe dementia (i.e., Clinical Dementia Rating Scale (CDR) score > 1) and contact with the closest proxy less than once every other week
- Not speaking or understanding Norwegian
- The GP does not want the particular patient to participate (in case of important reasons not covered by the other exclusion criteria)

In addition to these exclusion criteria listed in the study protocol, we have experienced some other reasons that lead to exclusion of patients: 1) deafness; 2) ongoing severe, acute illness; 3) not achieved contact with patient; 4) maximum number of patients already included in cluster.

Randomisation and blinding

GPs were recruited to participate in the study with patients from their lists. In order to avoid "contamination" between intervention and control patients, cluster randomisation on physician level instead of individual randomisation on patient level was performed. Because we wanted to

avoid large variation in cluster sizes, each GP could participate with a maximum of five patients. The GPs were stratified based on the number of contributing patients; 1-2 patients versus 3-5. Randomisation was computer generated and carried out in blocks of unknown and variable size. The allocation sequence was prepared by a statistician not involved in recruitment, and was made available to the researchers in sealed, opaque envelopes. In order to minimize the risk of selection bias, randomisation took place after inclusion of all patients within each cluster. The research assistant, who provided all the assessments, was blinded with respect to allocation. It was not feasible to blind the patients, their relatives or the GPs.

Primary endpoint

The primary endpoint is change in health-related quality of life (HRQoL), measured by the 15D instrument (single index version) at 16 weeks [2]. The single index, representing the overall HRQoL, varies between 0 (poorest HRQoL) and 1 (excellent HRQoL), and is calculated by using a set of population-based preference or utility weights. The 15D questionnaire was administered by patient interview. This was done by the research assistant, blind to group allocation. The 15D instrument is also validated for proxy raters. If the patient had moderate or severe dementia (CDR > 1), and/or the research assistant considered that they didn't understand the questionnaire, the 15D interview carried out with the closest proxy will be used as primary endpoint.

Secondary endpoints and background variables

Secondary endpoints and background variables are listed in Table 1. Secondary endpoints were assessed at baseline, 16 and 24 weeks. In addition, a set of descriptive background variables were registered at baseline.

Power calculation

The number of patients in the intervention group was planned to be approximately 100, and each GP could participate with 1-5 patients. The number of GPs (clusters) was therefore expected be 20-100 in the intervention group. A similar number of patients and GPs was planned to be included in the control group.

It was difficult to make valid assumptions on the correlation between patients within each cluster. In order to estimate the power of the study, we chose to estimate power in a worst case (perfect correlation) and a best case (no correlation) scenario. The true correlation was expected to be much closer to the latter, as the potential for intervention varies between individual patients. Based on previous studies using 15D, the standard deviation of change over time was expected to be between 0.07 and 0.08 [3-5]. The minimum important change (MIC) for the change in 15D scores is ± 0.015 [6]. A change of more than 0.035 in the negative direction represents "much worse HRQoL" and a change of more than 0.035 in the positive direction "much better HRQoL". Based on previous studies, in addition to a pilot study, we believed that our intervention was extensive enough to potentially improve the patients HRQoL to "much better" (> 0.035). As can be seen from Table 2, the power to detect a difference of 0.035 would then be in the range 59 to 94 %, and most probably > 80 %, provided that 100 patients were included in each treatment group.

Patient flow

Patient flow is illustrated in Figure 1.

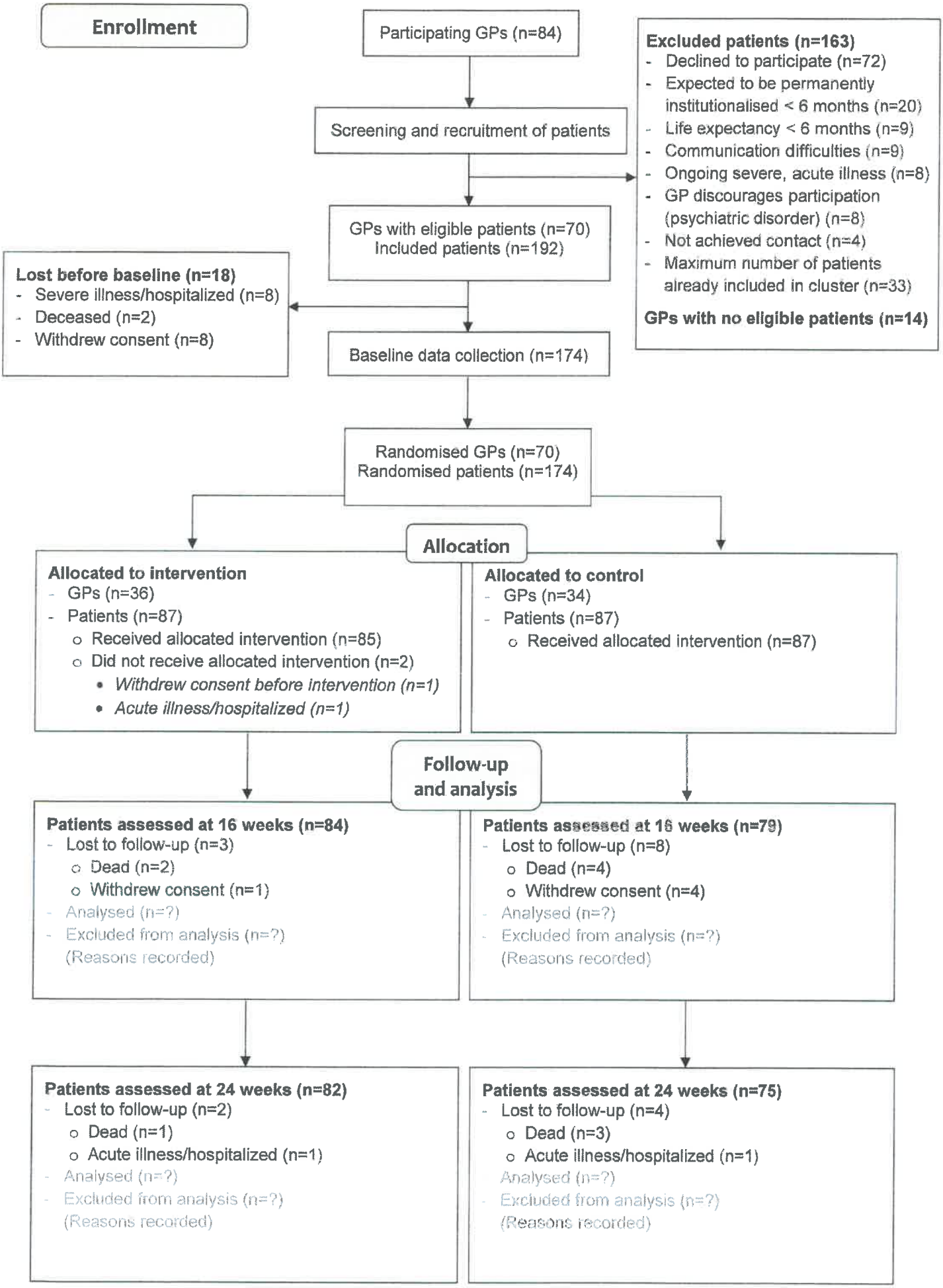

Figure 1 Patient flow

2. Primary endpoint analysis

The primary analysis will be done in the intention-to-treat population. The patients that were lost before baseline registrations will be excluded, as this occurred before randomisation.

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 and Altman [7], using 15D as the dependent variable and treatment group and cluster size as covariates. Due to the cluster randomised design, a robust estimate of the standard error with GP as the cluster will be applied.

We will also perform an analysis using a linear mixed model with GP as a random factor, time point (baseline, 16 and 24 weeks), treatment and the interaction between time and treatment as fixed factors, and cluster size as a covariate.

Both results will be reported, but the result by ANCOVA is our primary analysis. A p-value below 0.05 will be regarded as statistically significant, and focus will be on the estimated difference between the treatment groups, including 95% confidence intervals. Analyses will be performed in SPSS and Stata.

3. Handling of protocol violations

3.1 Wrongly included patients

A few patients using < 7 regular medications were included. The researchers could not check the number of medications before consent to participation was given, and in some cases it turned out that the GP or home nursing service had counted incorrectly. Medications could also be discontinued in the period from inclusion to baseline. We hypothesize that the potential for clinical improvements in the intervention group is better the more medications the patients use. We have therefore chosen to include these patients in the analysis, as it is likely that this will underestimate the effect of the intervention rather than overestimate it. There were no wrongly included patients for other reasons.

3.2 Patients not handled according to randomisation

Two patients in the intervention group were not handled according to randomisation. One withdrew consent before intervention, and one was hospitalized with severe acute illness and could not be approached. The patient that withdrew consent will be included in the analysis and handled with multiple imputation as described in 4.2. The hospitalized patient has completed the follow up-visits, and these measurements will be used. None of the patients in the control group were wrongly handled according to randomisation.

3.3 Timing of follow-up visits

Follow-up visits were planned at 16 and 24 weeks (± 2 weeks) after baseline. This was mostly followed, but in a few cases the date of the follow-up visit was exceeded by some days. These patients will however be included in the analysis, and their measurements will be used unchanged.

4. Handling of missing data

4.1 Missing responses on 15D

To derive the 15D score, there must be a response to each question (dimension). If a maximum of 3 responses are missing, we will use the imputation algorithm provided from the developers of the instrument (www.15d-instrument.net). If there are more than 3 missing values per observation, the 15D score will be left missing and will be handled by multiple imputation as described in 4.2.

4.2 Lost to follow-up

Patients who die before follow-up will be registered with the score "0" (worst possible HRQoL) on 15D. If patients are lost to follow-up for other reasons than death, they will be included in the primary analysis and missing values handled with multiple imputation using the mi procedure in Stata with M=5 imputations.

We plan to include the following variables in the imputation procedure:

- Age
- Sex
- Cumulative Illness Rating Scale (CIRS)
- Clinical Dementia Rating Scale (CDR)
- Use of home nursing service (minutes/week)

The set of variables may however depend on the pattern of missing values observed.

5. Sensitivity analysis

Missing values for the primary endpoint will be analysed in different ways in order to explore their potential influence on the results.

Analysis 1

Patients not handled according to randomisation and patients that are missing (all reasons) will be excluded (per protocol analysis).

Analysis 2

Patients missing for other reasons than death will be excluded, but deceased patients will be kept with the value "0" on 15D.

Analysis 3

Patients missing for other reasons than death will be handled as "last observation carried forward" (LOCF), but deceased patients will be kept with the value "0" on 15D.

6. Variables for adjustments

Variables with known or believed prognostic influence upon the outcome will be included in the analysis, one by one in addition to the randomisation group and cluster size. If their introduction to the model changes the effect estimate for the randomisation variable with 10% or more, they will be introduced in a final model including all variables with an effect of this size.

The following variables will be subject to such analyses:

- Age
- Sex
- Cumulative Illness Rating Scale (CIRS)
- Clinical Dementia Rating Scale (CDR)
- Use of home nursing service (minutes/week)

7. Secondary endpoint analysis

We will compare the intervention group with the control group with respect to the secondary endpoints listed in Table 1. For these analyses, we will use ANCOVA, linear mixed models (continuous data), Poisson regression (rare events) 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. Robust estimation of standard errors will be used to handle within-cluster (physician) correlation. For the secondary endpoints we will not perform impuation procedures for missing data – except from death, that will be given the lowest possible score. Results on some of the secondary endpoints might be published in separate papers.

8. Blind analysis

The study physician (RR) has performed the intervention and developed the databases, and may be able to understand from the data who the patient is and whether the patient belongs to the control or intervention group. The principal investigator (TBW) has also been involved in the intervention. The statistician (ES) made the randomisation sequence, and may be able to understand which clusters belong to the control or intervention group.

To maintain blindness and prevent bias due to the project administrator's expectations, we will therefore adhere to the following procedure: RR replaces all cluster numbers with new numbers and also allocates a random letter to patients in the intervention group and another to patients in the control group. This code is written and stored safely, and not delivered to ES. ES receives the dataset with these new cluster numbers and code for the randomisation variable, and carries out the primary analysis. When ES has finalised the statistical analyses, group allocation will be unmasked in a meeting where ES, TBW and RR all are present.

9. Tables

Table 1 List of secondary endpoints and background variables

Patient related endpoints
15D measured at 24 weeks
Short Physical Perfomance Battery (SPPB)
Gait speed
Hand grip strength (hand dynamometry)
Trail making test A + B
Five Digits Test
Digit Span
Falls
Orthostatic blood pressure
Weight
Functional Independence Measure (FIM)
All changes in pharmacotherapy
Medication Appropriateness Index (MAI)
Assessment of Underutilization (AOU)
Mortality
Family related endpoints
Relative Stress Scale (RSS)
Endpoints related to the local community and use of health services
Hospital admissions (with reasons)
Number of days in own home
Admission to permanent institutional care
Use of home nursing service (hours per week)
Background variables
Demographics
Diagnoses according to ICD-10
Cumulative Illness Rating Scale (CIRS)
Mini nutritional Assessment Short Form (MNA-SF)
Clinical Dementia Rating Scale (CDR)
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
Current drug use

Table 2 Estimation of power in different scenarios, provided a total of 200 participants

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 HRQoL index score
SD = Standard deviation of change over time in 15D score
r = Correlation between patients within each cluster

10. References

1. Romskaug R, Molden E, Straand J, Kersten H, Skovlund E, Pitkala KH, et al. Cooperation between geriatricians and general practitioners for improved pharmacotherapy in home-dwelling elderly people receiving polypharmacy - the COOP Study: study protocol for a cluster randomised controlled trial. Trials. 2017;18:158.
2. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. Ann Med. 2001;33:328-336.
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11. Signatures

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

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