Statistical study plan for the study Expand-Care

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This document is valid for the study protocol (version: *V 1.3)* of the study mentioned above.

Confidential

Condition for the services of the IMBS described in this statistical study plan is a cost-covering funding from the sponsor of the study (third-party funds) on the basis of a budget plan to be made by the IMBS.

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Statistical study plan

This statistical study plan is part of the study plan.

1. General

All statistical analyses except for the health economics evaluations and process evaluation are carried out by the Institut für Medizinische Biometrie und Statistik (IMBS) at the Universität zu Lübeck. All analyses are described in detail in the statistical analysis plan (SAP), which will be finalised before the registration of the last patient in the study.

2. Purpose, objectives and hypotheses of the study

Purpose of the study is to prepare a confirmatory clinical trial that will be adequately powered. The objective is the necessary precision of estimates of variation. As a consequence, a confidence interval of predefined width replaces hypotheses.

2.1 Purpose

Purpose of the study is to prepare a confirmatory clinical trial that will be adequately powered, smoothly conductible, and may be augmented by the evidence generated in the pilot study.

2.2 Objectives

Objective of the study is a narrow confidence interval for both, the population summary measure and the standard deviation of the outcome variable. The 6-months rate of hospital admissions in each group shall be estimated with a two-sided 95%-confidence interval that extends no more than 10 percentage points in either direction, as this would effectively restrict the range of possible sample sizes of the subsequent confirmation study. The 6-months incidence of hospitalisation of nursing home residents is thought to be 25% (Leutgeb et al., 2019). Using a rate of 30% or 20% in the control group as a basis for planning, sample size of the subsequent confirmatory study to detect a difference of 15 percentage points would change by 50%. If that rate was 25%, but the risk difference to be detected was 15% or 10%, one possible sample size would be 250% of the other, so that an interim analysis of the subsequent confirmatory trial could be justified or not.

2.3 Hypotheses

This pilot study will be used to define the hypotheses of the subsequent confirmatory study. They will have the form: There is no difference in the 6-months hospitalisation rates of nursing home residents cared for according to current standards or with the Expand-Care programme versus the risk difference is P1 % with P1 to be determined by the pilot study to be a number of perhaps 10 or 15.
Sample size planning of the pilot study could be thought of as being for a test of the hypotheses that 6-months hospitalization rates of nursing home residents cared for according to current standards is 25% versus 15% and with the Expand-Care programme 15% versus 25%.

3. Design of the study

3.1 General

The study will be national, bicentric, cluster-randomised, open, in parallel groups

3.2 Randomisation, blinding, confounding

Randomisation will be central to ensure concealment of allocation and will be stratified by time to balance any seasonal effects. Blinding is not possible in this complex intervention, but will be observed during statistical analysis and data review.

3.2.1 Registration and randomisation

The randomised allocation will be initiated after completion of the baseline assessment (t0) in participating nursing home residents by the investigators responsible for the respective nursing

homes. Participating nursing homes (unit of randomisation) will be randomised with an allocation ratio of 5:6 to the intervention or the control group. The random sequence will be generated by the IMBS by permutation with validated software once two nursing homes have faxed their readiness. So, date has to be stated on the fax asking for randomisation.
The trial statistician will write and test SAS code like

```
/* randomisation.sas
Reinhard Vonthein 18.03.2022 nach
Kundu & Roy auf lexjansen.com/pharmsug/2007/ad/AD07.pdf
Per stratum 3 blocks of size 2 */

data _null_;
 x=round(ranuni(0)*10000000);
 call symput ('seed', x);
run;

title1 "Seed number = &seed.";
title2 " Blocks are times of randomization,";
title3 "subject means nursing homes within a block in the temporal
order of their registration for randomization";

proc plan seed=&seed.;
 factors block=6 ordered subject=2 ordered/noprint;
 treatments treatment=2 random;
 output out=out
treatment cvals=('Expand-Care' 'Usual care');
run;

proc print data=out noobs;
 var block subject treatment;
 format subject z3.;
run;
```

for the generation of the randomisation sequence by permutation within time – the latter is called a block in the code. The effective randomisation sequence is generated, tested for balance (5:6 in total), and kept confidential by another person. Assignment of an institution is disclosed to just the designated investigator and only after registration, i.e. written assurance that all baseline assessments detailed in the protocol and other necessary preparations have been completed.
Registration and randomisation will be done via fax (++ 49 (0) 451 500-50614) from Monday to Friday from 08:00 to 14:00. Exceptions in which no randomisation is carried out are holidays and the period from 27.12. until 31.12. every year. The randomisation procedure is based on IMBS internal standard operating procedures.
The statistical analysis is prepared using place-holders assuming alternating assignments, so that results may not be guessed. True assignments are inserted into the code only after blinded review and data base closure.

3.2.2 Blinding

Due to the nature of the Expand-Care intervention, blinding of the nursing home residents and the nursing staff against the allocated intervention will be not feasible. However, in the information provided to the nursing home residents no specific hypotheses about possible directions of effects in measured outcomes will be described. The distal outcome data on hospital admissions, out-of-hour physician contacts and emergency service utilisation in the nursing home residents will be collected by study assistants blinded to the allocated intervention. For the assessment of all distal outcome (i.e hospital admissions, out-of-hour physician contacts, emergency service use and HRQoL) and resource use data in the nursing home residents, standardised instruments and

procedures will be used which have been proven feasible and reliable in previous trials of the authors (Müller et al. 2019, Richter et al. 2019). The trial statistician will be unaware of the assignments until after blinded review and data base closure. To this end, tests of the program code for analysis use an alternating assignment instead of the true allocation. The randomisation list will be merged to the data as a last step. A test of that step will use the list with alternating assignments.

3.2.3 Confounding

The primary endpoint is an event within 6 months, and the individual baseline measurement for this is the occurrence of the same event in the 3 months prior to randomisation. This will be observed retrospectively for adjustment in statistical analysis.
All analyses need to consider institution or one of its features as a moderator. This is usually done in the form of random effects/frailty to adequately model correlations. One exemption to this rule are the median differences and Hodges-Lehman confidence intervals, that take care of the problem by the resampling-like mode of their computation.

3.3 Endpoints

The hospitalisation rate measures a relevant burden to nursing home residents and from a payer perspective. Other measurements of resource use are complemented by residents' reports on quality of life, and safety outcomes. Morbidity endpoints will be used to describe the mechanism behind treatment effects.

3.3.1 Primary endpoints and hypotheses

The endpoint used in sample size calculation is the binary variable, whether a resident is hospitalised at least once during the six months following randomisation of the nursing home. All hospitalisations qualify irrespective of urgency, reason, duration, and initiator.
The primary estimand directly linked with sample size calculation is the difference of the proportion of such residents.
The endpoint for the first sensitivity analysis is the individual mean time between hospitalisations. All episodes between randomisation and hospitalisation or censoring and between discharge and re-hospitalisation or censoring are entered in a recurrent event analysis.
The endpoint for the second sensitivity analysis is the individual rate of hospitalisations (number divided by days in institution) within 6 months. This is analysed by Poisson regression with number of days in institution defining the offset.

3.3.2 Secondary endpoints

The list of endpoints is a subset of clinical investigation plan Tables 1, 2, 4.
(P) Occurrence of hospital admission within last 3 months at 3 and 6 months
(C) Number of hospital admission within last 3 months at 3 and 6 months
(C) Number of hospital days within last 3 months at 3 and 6 months
(P) Occurrence of out-of-hours physician contact within last 3 months at 3 and 6 months
(C) Number of out-of-hours physician contacts within last 3 months at 3 and 6 months
(P) Occurrence of emergency service use within last 3 months at 3 and 6 months
(C) Number of emergency service uses within last 3 months at 3 and 6 months
(M) EQ5D subscales and summary at 6 months
(M) 4DSQ subscales at 6 months
(P) Occurrence of falls within last 3 months at 3 and 6 months
(C) Number of falls within last 3 months at 3 and 6 months
(P) Occurrence of fall related injury within last 3 months at 3 and 6 months
(C) Number of fall related injuries within last 3 months at 3 and 6 months
(P) Occurrence of pressure ulcer of degree 2+ within last 3 months at 3 and 6 months
(P) Occurrence of pressure ulcer of degree 2 within last 3 months at 3 and 6 months

(P) Occurrence of pressure ulcer of degree 3 within last 3 months at 3 and 6 months
(P) Occurrence of pressure ulcer of degree 4 within last 3 months at 3 and 6 months
(P) Occurrence of incontinence associated dermatitis within 3 months at 3 and 6 months
(P) Occurrence of potentially inadequate medication within 3 months at 3 and 6 months
(M) Self-care subscales at 6 months
(M) Person-centredness subscales at 6 months
(T) Mortality within 6 months
(P) Occurrence of general practitioner visit within 3 months at 3 and 6 months
(C) Number of general practitioner visits within 3 months at 3 and 6 months
(P) Occurrence of specialist visit within 3 months at 3 and 6 months
(C) Number of specialist visits within 3 months at 3 and 6 months
(P) Occurrence of physiotherapy visit within 3 months at 3 and 6 months
(C) Number of physiotherapy visits within 3 months at 3 and 6 months
(P) Occurrence of occupational therapy visit within 3 months at 3 and 6 months
(C) Number of occupational therapy visits within 3 months at 3 and 6 months
(P) Occurrence of speech therapy visit within 3 months at 3 and 6 months
(C) Number of speech therapy visits within 3 months at 3 and 6 months
(P) Occurrence of rehabilitation visit within 3 months at 3 and 6 months
(C) Number of rehabilitation visits within 3 months at 3 and 6 months

(M) Time for PEPA training at 3 and 6 months
(M) Costs of PEPA training at 3 and 6 months
(M) 5 PEPA quality indicators at 6 months
(M) Time for other training at 6 months
(M) Costs of other training at 6 months
(M) Time for PEPA training per institution at 3 and 6 months
(M) Costs of PEPA training per institution at 3 and 6 months
(M) Time for other training per institution at 6 months
(M) Costs of other training per institution at 6 months
(M) Costs of medical devices and apps per institution at 6 months

3.4 Analysis timing

The statistical analysis will be prepared during the follow-up period and performed after monitoring, blinded review, and data base lock. No interim analyses are planned, not even for safety data.

4. Statistical analysis

4.1 Analysis population

The primary analysis population is defined by the intention to treat for all analyses including safety data, as the intervention is empowerment of carers rather than the actual application of the resulting methods of care.

4.2 Intercurrent events

Discontinuation of the Expand-Care intervention or adoption of a policy meant to reverse consequences of the Expand-Care intervention would affect whole institutions. Failure at PEPA training in single carers or at policy implementation are possibilities. Implementation of different policies is another possible intercurrent event.
Intercurrent events that may affect the individual participants are absorbing endpoints (permanent hospitalisation, death).

4.2.1 Analysis strategy

The default analysis strategy is the treatment policy strategy, i.e. intercurrent events are irrelevant as a rule. Absorbing endpoints are considered as competing risks or worst possible assessment by the composite strategy.

4.2.2 Estimands

The primary estimand of the marginal rates in treatment groups is estimated by mixed logistic regression from the occurrence of hospitalisation within 6 months on treatment and occurrence of hospitalization within 3 months prior to the trial (both fixed factors with two levels) and institution (random effects). All participants in all institutions are analysed by the assigned intervention irrespective of intercurrent events like incomplete policy enforcement. Death in the institution is counted as hospitalisation.
For the treatment effect:
The primary estimand is the marginal odds ratio of occurrence of hospitalisation within 6 months after randomisation adjusted for the presence of hospitalisation within the 3 months prior to the trial among all participants in all institutions by the assigned intervention irrespective of intercurrent events like incomplete policy enforcement. Death in the institution is counted as hospitalisation.
First sensitivity estimand is the hazard ratio of a Cox regression of recurrent events with shared frailty from times to hospitalisation on treatment and occurrence of hospitalisation within 3 months prior to the trial among all participants in all institutions by the assigned intervention irrespective of intercurrent events like incomplete policy enforcement. Death in the institution is counted as hospitalisation instead of as a competing risk.
Second sensitivity estimand is the marginal rate ratio of hospitalisation within 6 months in a mixed Poisson regression on treatment and occurrence of hospitalisation within 3 months prior to the trial among all participants in all institutions by the assigned intervention irrespective of intercurrent events like incomplete policy enforcement. Death in the institution is counted as hospitalisation.
All estimands above should be complemented by additional sensitivity estimands that employ GEE for GLM instead of random effects.

4.3 Descriptive statistics

The type of descriptive statistics used in this study are described in the following:

- Type C (count): Absolute frequencies of counts without adjustments and estimated marginal rates and 95% confidence interval for the marginal rate ratio from a mixed Poisson regression on allocated treatment with random institution effects (proc `genmod; ln log(n) model … / dist = poisson link = log offset = ln; repeated subject = institution / type = exch`).
- Type M (measurement): Median and range with 95% confidence Hodges-Lehmann intervals for the difference of medians.
- Type N (normal): Marginal means and total standard deviations (SD) for each treatment group and 95% confidence interval for the difference of marginal means all estimated using the mixed model with fixed treatment effect and random institution effects (proc `mixed; random`).
- Type LN (log-normal): Type N statistics are computed for logarithms and converted back to geometric means, ratio of geometric means and coefficients of variation.
- Type O (ordinal): Absolute frequencies without adjustments and estimated marginal probabilities and 95% confidence Wald interval for the odds ratio from a mixed ordinal logistic regression on allocated treatment with random institution effects (proc `glimmix; random intercept / subject = institution`).
- Type P (proportion): Absolute frequencies without adjustments and estimated marginal probabilities together with 95% confidence score interval for the difference of marginal proportions using a mixed logistic regression (proc `glimmix; random intercept / subject = institution`)..

Type T (time to event): Unadjusted Kaplan-Meier-curves, marginal cause specific hazard ratio (HR) with 95% confidence interval estimated from Cox-regression with shared frailty (proc `phreg; random`), and cumulative incidence functions for competing risks where needed.

The disposition of patients will be described by a CONSORT flow chart.

4.4 Overall methods of analysis

4.4.1 Testing strategy

The primary estimands, proportions in treatment groups, will be estimated into 95%-confidence intervals. Their odds ratio will be estimated into a 95%-confidence interval, too. Additionally, to adjust for multiplicity, (1 – 0.05/2) = 97.5%-confidence for the three will be calculated, as the third is fixed, if two are known. These are the results needed to plan a confirmatory study with the full confidence. They will be superseeded subsequently, so that they are not part of the second testing strategy.
This pilot study is not meant to confirm any claims, but may confirm some, nevertheless. In contrast to the subsequent confirmatory study, this pilot study will not primarily aim at the distal endpoints relevant to the patient, but rather confirm the mechanism of action by tests of the proximal endpoints describing changes in care. No interim analysis is planned with the aim of terminating the study early for efficacy or futility. This formal process evaluation will employ the Bonferroni-Holm procedure for the sixteen endpoints of the nine variables without adjustments, as most moderators will be measured after randomisation. The multiple significance level is set at 0.05, the first local significance level is set at 0.05/16, both for two-sided alternatives. As there was no power calculation directed at these tests, results have to be interpreted as tests of significance rather than tests between alternatives.
Conclusions other than those formulated above cannot be statistically ascertained. Confidence limits may, however, indicate what reasonable expectations are.

4.4.2 Methods of analysis

All analyses are described in detail in the statistical analysis plan (SAP), which will be finalised before the registration of the last patient in the study. The analyses specified therein will be translated into computer code. The results of that code applied to the closed data base are the basis for the statistical study report, on which the clinical study report will be based.
Analyses like the ones in 4.3 will be adjusted for baseline measures of the same, if measured, or by age in the case of mortality. The mapping of endpoints to analysis type is indicated in the list 3.3.2 above by abbreviations of types in parentheses.

4.5 Sample size calculation

A total of 11 nursing homes are to be included, with an average of 15 participating residents. These will be randomised with chance 5:6 to the intervention group and to the control group, resulting in 75 and 90 study participants per study arm. With an assumed drop-out rate of max. 20% (Richter et al., 2019, Saal et al., 2019), data of 60 and 72 residents for each study arm are expected.
The sample size calculation is based on the following assumptions: With an average of 50 residents per nursing home (Statistisches Amt für Hamburg und Schleswig-Holstein, 2020) and an assumed rate of approx. 60% residents meeting eligibility criteria (clinical estimate based on epidemiological data on the incidence of hospital admissions (Leutgeb et al., 2019) and emergency room visits (Brucksch et al., 2018)), it is assumed that on average 60%, i.e. 30 residents, are potentially eligible for participation. Assuming a participation rate of 50% among these residents (Saal et al., 2019), an achievable mean cluster size of 15 residents is assumed. Considering an intra-cluster correlation coefficient of 0.021 (Adams et al., 2004, Richter et al., 2019), this mean cluster size results in a design factor (inflation factor) of 1.294, i.e. the assumed number of 60 and 72 residents with analysable

outcome data corresponds to an effective analysable sample of 46 and 55 residents per treatment group.
The aim of the present study is to estimate as precisely as possible the proportion of residents with at least one hospital admission during the six-month observation period in each of the two treatment groups. Based on empirical results on the annual incidence of hospital admissions among nursing home residents (Leutgeb et al., 2019), it is assumed that the proportion of residents with at least one hospital admission in the control group will be 25% (i.e. 0.25 rate of hospital admissions) for the six-month observation period in this study. Furthermore, it is assumed that the Expand-Care programme to be tested in the intervention group can realistically lead to a reduction in the incidence by a maximum of 10% to 15% (= 0.152 rate of hospital admissions) within the six-month observation period. The planned sample sizes allow these rates to be estimated with a confidence interval of +/- 0.115 or +/- 0.119 in the control group and +/- 0.095 or +/- 0.0985 in the intervention group. This is considered to be sufficient for a precise calculation of the required sample size for subsequent explanatory randomised controlled trials.

4.6 Interim analyses and design adaptions

4.6.1 Interim analyses

No interim analysis is planned, so that any interim analysis would be preceded by an amendment to the trial protocol.

4.6.2 Design adaptions

No design adaption is planned, so that any design adaption would be preceded by an amendment to the trial protocol.

4.7 Adjustment and stratification

The analyses of endpoints will be adjusted for the respective baseline observations and will correct for correlated observations within institutions by random effects models and by GEE as sensitivity analyses.

4.8 Subgroup analysis

The primary analysis will be complemented by subgroup analyses that are exploratory in nature. The results will be displayed as a forest plot of confidence intervals for odds ratios within subgroups, absolute frequencies, and descriptive P values of the statistical tests for interaction between the grouping variable and the treatment. Subgroups will be defined by the baseline values of binary outcome variables and some plausible predictors, if subgroup sizes reach at least 20:
Occurrence of hospital admission within last 3 months
Level of care needed (Pflegegrad) at baseline (care level 2 versus 3 or higher)
Number of comorbidities in classes of at least 20 participants
Dementia Screening Score </=4 versus >4 at baseline
Two classes of maximum number of persons cared for at the institutions
Degree of implementation of Expand-Care programme as quantified in the process evaluation pooled to groups of at least 3 institutions
Occurrence of out-of-hours physician contact within last 3 months
Occurrence of emergency service use within last 3 months
Occurrence of falls within last 3 months
Occurrence of fall related injury within last 3 months, if at least 20 participants
Occurrence of pressure ulcer within last 3 months
Occurrence of incontinence associated dermatitis within 3 months
Occurrence of potentially inadequate medication within 3 months
Occurrence of specialist visit within 3 months
Occurrence of physiotherapy visit within 3 months
Occurrence of occupational therapy visit within 3 months

Occurrence of speech therapy visit within 3 months
Occurrence of rehabilitation visit within 3 months
Sex
Region (HL or HH).
Interpretation of implementation groups would be even more tentative than the rest of the hypothesis generating subgroup analyses, as this happens after randomisation and groups are formed so as to be extreme. An exploratory mediator analysis should be tried instead.

4.9 Missing data

Missing observations in random effects analyses are not imputed. The only exception are "worst case" imputations of hospitalisations in case of death in the institution, when death is not a competing risk. That is a conservative assumption to prevent death from being a favourable outcome. Subjective assessments that were collected earlier than 77 days after randomisation or later than 207 days after randomisation will be set to missing, as the former could severely bias the treatment effect in case of a missing assessment at t2 and the latter would not capture the effect of the intervention that is considered discontinued by then.

4.10 Safety analyses

Medical treatments will be reported. Their frequency will be tabulated by treatment and kind rather than system organ class. The extraction from the eCRF is complex, as the information is scattered. Types are:

- Emergency service, if ambulance or emergency physician, but not just a phone call
- Contact with general practitioner,
- Unplanned visit of general practitioner,
- Visit at the general practitioner's,
- Contact with specialist,
- Physiotherapy,
- Ergotherapy,
- Logopaedic therapy,
- Osteopathy.
- others

Complications:

- Falls,
- Pressure ulcer,
- Dermatitis caused by incontinence
- Deterioration of care level

will be tabulated by randomised treatment and degree or damage. Duration of pressure ulcers and dermatitis will be described by treatment group.
Hospitalisations that are not planned will be tabulated by category (rather than system organ class), duration, outcome, and treatment. Mortality will be tabulated by treatment and cause of death.
Hospitalisations that could have a causal association with the intervention will be listed with all available data and additional information on mitigating treatment.

4.11 Health services research

Medical treatments and requests for these will tabulated by function of the person that initiated the contact, whether the need newly arose, whether the requested treatment was delivered, and the means used.

Complications:

Falls,
Pressure ulcer,
Dermatitis caused by incontinence,
Deterioration of care level
will be tabulated by randomised treatment and requested treatment of the complication.

4.12 Exploratory and sensitivity analyses

The effect of missing data on occurrences is explored by sensitivity analyses of individual incidence rates (Poisson Regression) and event times (Cox regression). This applies to the endpoints that may occur more than once:
Times to or number of out-of-hours physician contact within 6 months
Times to or number of emergency service use within 6 months
Times to or number of falls within 6 months
Times to or number of fall related injury within 6 months
Times to or number of pressure ulcer of category 2+ within 6 months
Times to or number of pressure ulcer of category 2 within 6 months
Times to or number of pressure ulcer of category 3 within 6 months
Times to or number of pressure ulcer of category 4 within 6 months
Times to or number of incontinence associated dermatitis within 6 months
Times to or number of potentially inadequate medication within 6 months
Times to or number of AE within 6 months
Times to or number of SAE within 6 months
Times to or number of general practitioner visit within 6 months
Times to or number of specialist visit within 6 months
Times to or number of physiotherapy visit within 6 months
Times to or number of occupational therapy visit within 6 months
Times to or number of speech therapy visit within 6 months
Times to or number of rehabilitation visit within 6 months

Further adjusted and mediation analyses should explore the need for more or less data in any subsequent trial.

5. Reporting and publication

Reporting will adhere to the CONSORT statement.
Results from the study will only be published after the database has been closed with the only exceptions being publications concerning the design of the study. Before, for methodological-statistical reasons, it must only be reported in general form without results, e.g. recruitment status or demographic characteristics of study participants (within the meaning of Table 1 of a study). There will be no publications or conference contributions on outcomes prior to the first publication on the primary outcome that encompasses the results from all participating institutions.
Any publication shall be consented among the authors and the coordinating investigator. All reports and publications concerning the study are agreed with the responsible biostatistician of the IMBS in order to avoid misinterpretations of statistical results. Conclusions or recommendations formulated in the publications for which a statistical assurance is claimed require the consent of the statistical co-authors. Conclusions or recommendations for which no statistical coverage is claimed are expressly designated as such at the request of the statistical co-authors (see, for example: Grundsätze für die ordnungsgemäße Durchführung der klinischen Prüfung von Arzneimitteln. 9.12.1987. Bundesminister für Jugend, Familie, Frauen und Gesundheit, Bundesanzeiger Nr. 243 vom 30.12.1987, S. 16167, Punkte 4.2. und 4.2.5, and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH-Efficacy Topic 3, Structure and Contents of Clinical Study Reports, Annex VIII, point A d) (ii)).

A study-assisting member of the IMBS or the ZKS is second on the authors list and the senior author of the IMBS or ZKS second to last in the authors list. Further co-authorships of the IMBS and ZKS are based on the Good Scientific Practice Guideline of the DFG and the four rules of the ICMJE.
The data from the respective centre will be made available to investigators upon request at the end of the study. Publication of this study data from individual centres is only possible after publication of the overall study results.

6. Literature

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