STATISTICAL ANALYSIS PLAN

Study title: A multi-centre randomised controlled trial to compare the effectiveness of admission avoidance hospital at home with comprehensive geriatric assessment vs. inpatient comprehensive geriatric assessment on the number of frail older people 'living at home'

Short title: Randomised controlled trial (RCT) of comprehensive geriatric assessment (CGA) in a hospital at home (HAH) setting

Ethics ref: 14/WA/1081 (England, Wales & Northern Ireland); 14/SS/1046 (Scotland)

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1.0	15 March 2019	Original version

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1 INTRODUCTION

1.1 PREFACE

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This SAP supports version 4.1 of the protocol dated 19 April 2018

1.2 PURPOSE AND SCOPE OF THE PLAN

This document details the proposed analysis of the main paper(s) reporting results from the NIHR Health Services Research and Delivery programme funded randomised controlled trial exploring the effectiveness of comprehensive geriatric assessment (CGA) in a home or hospital setting. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

The details regarding analysis of the cost-effectiveness, process evaluation and qualitative study will be detailed in a separate analysis plan.

The CGA trial will be analysed after the 6 months follow-up data has been collected and before 12 months follow-up. The analysis of 12 month follow-up data will be reported in a separate statistical analysis report to the main trial findings (i.e. 6 month outcome).

1.3 TRIAL OVERVIEW

Hospital admissions among older adults with frailty are increasing. The evidence supporting the adoption of acute care is from small trials, and it is uncertain if acute care in the home with CGA improves health outcomes or reduces cost compared with inpatient admission with CGA.

1.4 OBJECTIVES

The primary objective in the protocol outlines both the effectiveness and cost-effectiveness of admission avoidance. The secondary objective focuses on a process evaluation. All objectives related to health economics will not be mentioned or detailed in this analysis plan.

Primary Objective

1. To test the effectiveness and cost-effectiveness of admission avoidance hospital at home (HAH) with CGA compared with hospital admission with CGA and investigate the generalizability and cost-effectiveness of CGA in settings where health and social care provision vary.

Secondary objectives

All objectives unrelated to the main statistical analysis and will be outlined elsewhere.

2 TRIAL DESIGN

The study is a multi-site open randomised controlled trial. Participants will be randomised using a 2:1 ratio to either the intervention arm of admission avoidance HAH with CGA or the control arm of hospital inpatient CGA. The patient population is older people with frailty and a level of disability, who are the target population for HAH services.

Sites are Bradford, Newport & Torfaen, Lanarkshire, Lothian, Fife, Royal Devon Exeter, North Devon, Southern Trust, Guys & St. Thomas, and Belfast.

See Appendix I for a time schedule of trial procedures.

2.1 OUTCOMES MEASURES

Outcomes are measured at baseline, 6 months and 12 months (excluding delirium which is measured at 3 days, 5 days and 1 month) after randomisation. Data will be entered directly onto CRFs and e-CRFs

See Appendix II for a table of outcome assessment schedule.

2.1.1 PRIMARY OUTCOME FOR THE PRIMARY OBJECTIVE

The primary outcome is 'living at home' at 6 months.

Living at home is defined as the inverse of death or living in a residential care setting. It is derived from a place of assessment variable, (a 5-category variable, 1 = hospital assessment centre, 2 = in-patient hospital, 3 =

residential care home, 4 = patient's home, and 5 = other) and the patient's death status (0 = alive, 1 = dead) reported at the 6 months visit. Living at home will be coded as a binary variable (1 = alive and living at home, 0 = otherwise (including deaths and living at residential care). Living at home will be computed as 0 if death status = 1 (dead) or place of assessment = 3 (residential care home), or place of assessment = 5 (other) and other = "Nursing Home" (variable *assessoth6m*), otherwise living at home = 1, as long as patient also has a visit date for the particular time point.

Additional information about the residential care (variable *admitryr*) will be used for patients with a place of assessment = 1 (hospital assessment centre) or = 2 (in-paint hospital) to verify where these patients were admitted from. If patients have been in residential care they will be coded as 'not living at home', if patients are not recorded as having been in residential care then they will be assumed to have been admitted from 'home'.

If the patient's death status is missing and the patient's place of assessment has been completed, the patient will be assumed to be alive. In cases were the place of assessment and death status are conflicting (i.e. place of assessment is complete but the patient has been reported as dead) then the patient death form CRF will be used to confirm whether the patient is alive or dead. If the place of assessment and the patient's death status are both missing, then the primary outcome will be missing. This information will be coded as a binary variable (0 = death or not living at home, 1 = alive and living at home) to be used in the analysis.

2.1.2 SECONDARY OUTCOMES FOR THE PRIMARY OBJECTIVE

The secondary outcomes for the primary objective are: presence of delirium, mortality, new long-term residential care, cognitive impairment, activities of daily living, quality of life, quality adjusted survival, length of stay in hospital, readmission or transfer to hospital, resource use (health and social care and informal care), and costs and cost-effectiveness, see Appendix III for questionnaire scoring.

1) **Incident and Persistent of Delirium (CAM) at baseline, 3 days, 5 days, and 1 month**
   The Confusion Assessment Method (CAM) diagnostic algorithm [1] is used to derive a variable for delirium, and is assessed at baseline, 3 days, 5 days and 1 month follow-up. CAM is split into 4 features (acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness).
   Feature 1 (acute onset and fluctuating course) is present if there is evidence of an acute change in mental status from the patient's baseline (variable *cam1*) **AND** the behaviour fluctuated during the interview (variable *cam2b*). Feature 2 (inattention) is present if the patient had difficulty focusing attention during the interview in either mild or marked form (variable *cam2a*). Feature 3 (disorganized thinking) is present if the patient's thinking is disorganised or incoherent (variable *cam3*). Feature 4 (altered level of consciousness) is present if the patient's level of consciousness is anything other than alert (or uncertain) (variable *cam4*).
   A diagnosis of delirium will be coded as a binary variable (0 = absent, 1 = present) and is present if the patient is positive for a presence of acute onset and fluctuating discourse (feature 1) **AND** positive for inattention (feature 2) **AND EITHER** disorganised thinking (feature 3) **OR** altered level of consciousness (feature 4).
   If 'not applicable' is answered it shall be treated as 'no', and delirium will be calculated for each patient unless all the items from these sections are missing, in this case the delirium score will be coded as missing.

2) **Mortality at 3 days, 5 days, 1 month, 6 months and 12 months**
   Patient mortality status is collected at 3 days, 5 days, 1 month, 6 months and 12 months after randomisation on the respective follow-up CRFs, date and details of a patient's death is collected on

the patient death form CRF. If a patient has been reported as dead at 6 or 12 months on the follow-up CRF (variable *deathyn*) it will be checked against the date of death on the Patient Death CRF (variable *deathdat*). If there is conflicting information between the follow-up form and the death form, the death form will overrule the Follow up CRF. If neither the follow-up form nor the death form have been completed then the TM will check with the site if the patient has died.

3) New long-term residential care at 1 month and 6 months

Subsequent admission to residential care is measured at 1 month, and 6 months follow up (variable *admitryn*). This will be coded as a binary variable (0 = No, 1 = Yes). The 6 months admission to residential care data will include the data collected at the 1 month time point.

4) Cognitive impairment at baseline and 6 months (MoCA)

The Montreal Cognitive Assessment (MoCA) [2] is used to derive a variable for cognitive impairment, and is assessed at baseline and 6 months follow-up. The MoCA comprises 8 sections with a total of 30 questions administered by a qualified health professional (variables *mocavis mocanam mocaatt mocalan mocaabs mocarec mocaori*). A total MoCA score will be derived by summing the score from each section of the questionnaire, only patients with complete MoCA will have a total MoCA score computed, an extra point is added to the total score if the patient has 12 or less years of education. The possible range of scores for the MoCA range from 0 to 30, with a score of 26 or above is considered normal. If the patient is visually impaired or if they are frail and unable to write and draw, the visuospatial/executive section (variable *mocavis*) and the naming section (variable *mocanam*) are excluded and is scored out of 22 instead, a score of 18 or above is considered normal.
Cognitive impairment will be coded as a binary variable (0 = score less than 26 (less than 18 if visually impaired), 1 = score 26 or more (18 or more if visually impaired).

5) Activities of daily living at baseline and 6 months (Barthel index)

The Barthel index [3] is used to derive a variable for activities of daily living, and is assessed at baseline and 6 months follow-up. The Barthel index consists of 10 questions (variables *biadl1* – *biadl10*), and has a possible range of scores from 0 (completely dependent) to 20 (completely independent). The final Barthel index score is derived by summing the 10 items.

6) Known cognitive decline at baseline (IQCODE)

The Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [4] is assessed at the patients baseline visit only. IQCODE is a 16 item questionnaire (variables *iqcode1* – *iqcode16*), each question has a possible range of scores from 1 to 5. To obtain the mean IQCODE score for each participant take the mean of all IQCODE items available for that participant. Participants will still have their mean IQCODE score calculated if they are missing several items, participants will only be missing their mean IQCODE score if they are missing every item. Randomisation was stratified by IQCODE score ≥ 3.5

7) Quality of life at baseline and 6 months

Quality of life is measured by EQ-5D-5L scores [5], and is assessed at baseline and 6 months follow-up. EQ-5D-5L index scores will be computed as per the EQ-5D-5L user guide (version 2.1 April 2015).

8) Quality adjusted survival at 6 months and 12 months

Quality adjusted survival will be analysed as part of the economic evaluation and the methods will be detailed in a separate analysis plan.

9) Length of hospital stay over 6 months from randomisation

Number of nights spent in hospital between baseline and 6 months follow-up is collected on the health service use CRF.

10) **Readmission or transfer to hospital at 1 month and 6 months**
Subsequent admissions to hospital is measured at 1 month, and 6 months follow-up (variable *hadmityn*). Subsequent admissions to hospital is a binary variable (0 = No, 1 = Yes). The 6 months admission to hospital data will include the data collected at the 1 month time point. Number of days spent in hospital at 1 month, and 6 months after baseline will not be considered in the main statistical analysis, this data will be analysed as part of the economic evaluation and the methods will be detailed in a separate analysis plan.

11) **Resource use (health and social care and informal care) at baseline and 6 months**
Resource use will be analysed as part of the economic evaluation and the methods will be detailed in a separate analysis plan.

12) **Costs and cost-effectiveness**
Costs and cost-effectiveness will be analysed as part of the economic evaluation and the methods will be detailed in a separate analysis plan.

13) **'Living at home' at 12 months**
Data on living in residential care and death will be collected from a range of sources, this will include the primary care and hospital record. Patient's GPs may be followed up over 12 months to collect information on admission to hospital and death. If this happens this outcome will be derived as per the primary outcome using place of assessment and patient's death status reported at the 12 months visit.

2.2 TARGET POPULATION

Inclusion Criteria

- Participant is willing and able to give informed consent for the participation in the study.
- If the participant lacks capacity to consent they have a relative or friend who is a 'personal consultee' or Independent Mental Capacity Advocate who will be invited to advise on whether they believe that participation in the study would be in accordance with the values and interests of the individual.
- Male or Female, aged ≥ 65 years.
- Patient had been referred to the admission avoidance HAH service with CGA and would otherwise require hospital admission for an acute medical event. This will include patients presenting with delirium, functional decline, dependence, falls, immobility or a background of dementia presenting with physical disease.
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.
- English speaking.

The presence of a carer will not be a requirement for enrolment and will depend on the individual circumstances of the patient; this will be at the discretion of the clinician responsible for the patient, as is current clinical practice in each centre.

Exclusion Criteria

- Patients with acute coronary syndrome, this includes myocardial infarction and unstable angina and is characterised by cardiac chest pain and is associated with ECG changes.
- Patients presenting with symptoms which require an acute surgical assessment.
- Patients with a suspected stroke.
- Patients who are receiving end of life care as part of a palliative care pathway.
- Patients who refuse HAH service.
- Patients considered by the clinical staff to be too high risk for home based care, for example those who are physiologically unstable, who are at risk to themselves or if the carer reports HAH care who not be acceptable (in keeping with existing clinical practices for HAH).
- Patients living in a residential setting.

2.3 SAMPLE SIZE

The sample size is calculated for the primary outcome: living at home at 6 months follow up (the inverse of death or living in a residential care setting), for a 2:1 randomisation ratio with 2/3rd randomized to admission avoidance HAH with CGA and 1/3 to inpatient CGA. Several sources informed our estimate of effect size; these were one of the trials included in the IPD meta-analysis of HAH which recruited frail older people who required hospital level care (similar to the study population we plan to recruit), an audit of 750 patients who received HAH + CGA in Lanarkshire, the RCTs of CGA included in the Cochrane Review and the pooled estimate for the relative effect at 6 months obtained from the IPD Cochrane Review of HAH (3 trials, 607 participants) which was an adjusted Hazard Risk of 0.62 (95% CI 0.45 to 0.87) for mortality. Our proposed study effect estimate is based on a control group (CGA hospital) event rate at 12 months of 50% with a 10% reduction in living in a residential setting to 40% in the CGA at home group, equal to a relative risk of 0.8 which lies towards the top end of the 95% CI for the pooled estimate. We have calculated that a sample size of 1050 to achieve around 83% power at a significance level of 0.05 to detect a 10% absolute difference, assuming a control group event rate at 12 months of 50% and 6% attrition.

2.4 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

Following informed consent and the collection of baseline data eligible patients will be randomly allocated using a 2:1 ratio (2 admission avoidance HAH with CGA: 1 inpatient CGA) by the local member of the research team who recruited the participant. Randomisation will be performed using Sortition, Oxford University's Primary Care Clinical Trail Unit's in-house online randomisation system. Randomisation will be stratified by centre (Bradford, Newport Lanarkshire, Lothian, Fife, Royal Devon Exeter, Torfaen, North Deon, Southern Trust, Guys & St. Thomas, and Belfast), gender and by known cognitive decline.

We have opted for a 2:1 ratio as the HAH schemes have been established to ease the pressure on acute hospital beds and concern was expressed by the clinical leads that a 1:1 randomisation ratio would place unmanageable pressure on the inpatient service. This was therefore a decision related to the capacity of the service to manage patients in the two settings. This has been taken into account in our analysis plan and will not affect the estimated precision of our findings.

Due to the nature of the intervention, it is not possible to blind participants. It will also not be possible to blind research nurses who will collect outcome data as participants will know which intervention they will have received (admission avoidance HAH with CGA or inpatient admission) and are likely to discuss this with the nurse.

3 ANALYSIS – GENERAL CONSIDERATIONS

3.1 DESCRIPTIVE STATISTICS

Frequencies (with percentages) for binary and categorical variables and means (with standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented.

3.2 CHARACTERISTICS OF PARTICIPANTS

Baseline characteristics of participants (age, gender, education, place of assessment, consent signed by consultee, presenting problem and diagnosis) and baseline outcome data; co-morbidity (Charlson index), activity of daily living (Barthel index), cognitive impairment (MoCA), cognitive status (IQCODE), health status (EQ5D), and delirium (CAM) will be summarised for both randomised groups. There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variables.

Patient throughput from screening through randomisation, follow up and analysis will be presented in a CONSORT flow chart (Appendix IV).

3.3 DEFINITION OF POPULATION FOR ANALYSIS

All data will be included in the analysis as far as possible to allow full ITT analysis. Patients will be analysed in the groups they were allocated, irrespective of whether they received that intervention or not.

3.4 POOLING OF INVESTIGATIONAL SITES

Analysis will not be pooled as the primary and secondary analysis sufficiently account for the different centres.

3.5 DATA MONITORING COMMITTEE AND INTERIM ANALYSES

The trial is of a method of management rather than a medicinal product and it is not anticipated that the trial will be terminated unless on the advice of the Data Monitoring Committee (DMC) in the case of a series of Suspected Unexpected Serious Adverse Reactions (SUSARs).

No interim analysis was planned in the protocol.

A separate document details the data/information which will be presented in the DMC report (located: K:\HB_O\CGA\STATS\3. TSC and DMC\DMC\DMC report template)

4 PRIMARY ANALYSIS

The primary objective is to test the effectiveness of admission avoidance HAH with CGA compared with CGA and investigate the generalizability of CGA in settings where health and social care provision vary.

4.1 PRIMARY OUTCOME

The primary outcome is living at home at 6 months follow-up. A generalised linear mixed model will be fitted to the data with living at home at 6 months as the dependent variable. The model will include intervention arm, gender, and known cognitive decline (IQCODE, the full score will be included in the model) as fixed effects, as well as stratification factors; centre as a random effect. If sites recruited only a small number of patients to the study then these will be grouped together in an 'other' category for the random effect. The

adjusted relative risk between randomised groups with 95% confidence intervals and p-value for living at home at 6 months will be derived from the model.

4.2 HANDLING MISSING DATA

The frequency (with percentage) of losses to follow-up (defaulters and withdrawals) over the 6 months of the study will be reported by randomised group and compared between the groups.

The availability of the outcome data for the primary outcome will be summarised by randomised group. The generalised linear mixed model implicitly accounts for data missing at random, however the data missing mechanism will be explored. A logistic regression model will explore any association between baseline characteristics and availability of the primary outcome.

Any changes to the assumptions made in the primary analysis i.e. data missing at random, will be considered in a sensitivity analysis.

The impact of any missing primary outcome data on the primary analysis will be assessed by carrying out a sensitivity analyses based on imputing (multiple imputation) the missing values.

4.3 HANDLING OUTLIERS

Any outliers will be checked and verified to ensure that they are true values. No statistical analysis will be conducted to assess the impact of potential outliers on the results.

4.4 MULTIPLE COMPARISONS AND MULTIPLICITY

The primary outcome is clearly stated in the protocol and no adjustment for multiple comparisons will be made.

4.5 MODEL ASSUMPTIONS

Model assumptions will be assessed using graphical representation of residuals. If the assumptions for the primary analysis are not satisfied, a non-parametric test, such as a chi-squared test or Fisher's Exact Test will be used.

5 SECONDARY ANALYSIS

5.1 SECONDARY OUTCOMES

1) **`Living at home` at 12 months**
   The 'living at home' at 12 months outcome will be analysed separately from the 6 months analysis (since the main analysis shall be carried out after 6 months but before the 12 months follow-up data has been collected) and will not be reported in the main report, instead it will be reported in a separate statistical analysis report. The data will be analysed using a generalised linear mixed models as described in section 4.1, with 'living at home' at 12 months as the outcome. The intervention effect with 95% confidence interval and p-value will be reported.

2) **Presence of delirium at 3 days, 5 days, and 1 month (CAM)**
   Presence of delirium is assessed at baseline, 3 days, 5 days, and at 1 month, by the Confusion Assessment Method (CAM) and is a binary variable. A generalised linear mixed model will be used similar to the primary analysis (section 4.1) with presence of delirium at 3 days and 5 days, and

presence of delirium at 1 month as the dependent variable. The model will include intervention arm, baseline CAM, stratification factors (gender and known cognitive decline (IQCODE)) as fixed effects; and centre as a random effect. The model will also include a random interception for each patient. The model will include an interaction between time and randomised group as a fixed effect. The adjusted relative risk between randomised groups with 95% CI and p-value for presence of delirium at 3 days, 5 days, and at 1 month will be estimated from the model.

3) Mortality at 6 months and 12 months

Mortality is measured at 3 days, 5 days, 1 month, 6 months, and 12 month follow-up (*deathyn*) and is a binary variable (0 = dead, 1 = alive). The mortality outcome will be summarised at each time point but will only be analysed at 6 and 12 months. The mortality at 12 months outcome will be analysed separately from the 6 months analysis and will not be reported in the main report, instead it will be reported in a separate statistical analysis report. Mortality at 6 months will be reported in the main statistical analysis report. A generalised linear mixed model will be fitted to the data similar to the primary analysis (see section 4.1) with mortality as the dependent variable. The model will include intervention arm, stratification factors (gender and known cognitive decline (IQCODE)) as fixed effects; and centre as a random effect. The adjusted relative risk and 95% CI and p-value for mortality at each time point will be estimated from the model. Mortality at 12 months will be analysed similar to the 6 months mortality data.

4) New long-term residential care at 1 month and 6 months

New long-term residential care is measured at 1 month and 6 months follow-up (*admitryn*) is a binary variable (0 = No, 1 = Yes). A generalised linear mixed model will be fitted to the data with new long-term residential care at 1 and 6 months as the dependent variable. The model will include intervention arm, gender, and known cognitive decline (IQCODE) as fixed effects, and centre as a random effect. The model will include a random intercept for each patient. The model will include an interaction between time and randomised group as a fixed effect. The adjusted relative risk with 95% CI and p-values for new long-term residential care at 1 month and 6 months will be estimated from the model.

5) Cognitive impairment at 6 months (MoCA)

Cognitive impairment measured at baseline and 6 months by the Montreal Cognitive Assessment (MoCA). This is converted into a binary variable (see section 2.1.2). A generalised linear mixed model will be fitted to the data with cognitive impairment at 6 months as the dependent variable. The model will include intervention arm, baseline MoCA score, gender, and known cognitive decline (IQCODE) as fixed effects; and centre as a random effect. The adjusted relative risk with 95% confidence intervals and p-value for cognitive impairment at 6 months will be estimated from the model.

6) Activities of daily living at 6 months (Barthel index)

Activities of daily living is measured at baseline and 6 months by the Barthel index and is a continuous variable. A linear mixed effects model will be fitted to the data with activities of daily living at 6 months as the dependent variable. The model will include intervention arm, baseline Barthel index score, gender, and know cognitive decline (IQCODE) as fixed effects, as well as centre as a random effect. The intervention effect with 95% confidence intervals and p value for activities of daily living at 6 months will be estimated from the model.

7) Readmission or transfer to hospital at 1 month and 6 months

Readmission or transfer at 1 month and 6 months (*hadmityn*) is a binary variable (0 = No, 1 = Yes). A generalised linear mixed model will be fitted to the data with readmission or transfer to hospital at 1

and 6 months as the dependent variable. The model will include intervention arm, gender, and known cognitive decline as fixed effects, and centre as a random effect. The model will also include a random intercept for each patient. The adjusted relative risk with 95% CI and p-values for activities of daily living at 1 month and 6 months will be estimated from the model.

The distribution of the models will be assessed and the assumptions of the models will be checked. If any of the assumptions are violated the first option would be to apply a suitable transformation to the data, if this is not possible then a non-parametric test will be applied to the data (i.e. chi-Squared test). If a non-parametric test is adopted, it will not be possible to adjust for covariates.

5.2 TERTIARY/OTHER OUTCOMES

Analysis of other outcomes (i.e. cost-effectiveness, process evaluation and qualitative interviews) will be detailed elsewhere.

6 SENSITIVITY ANALYSIS

Sensitivity analysis will be conducted with respect to the primary outcome only (unless explicitly stated) and will explore the sensitivity of results to different assumptions regarding missing data, outliers and departure from randomisation policy.

1) The generalised linear mixed model assumes that the data is missing at random (MAR). A logistic regression analysis will be conducted to investigate factors at baseline (if any) that are predictive of non-response. If any factors are associated with non-response, the generalised linear mixed model in the primary analysis will be re-run with these factors included as fixed covariates in the model.

2) Some patients might have missing data for the 'living at home' at 6 months outcome due to missing place of assessment and/or death status. These patients will have their missing place of assessment and/or death status replaced with each of the alternatives for these variables:
    i) Living at home and alive
    ii) Not living at home and alive
    iii) Dead

    The 'living at home' at 6 months outcome will be re-derived, and the generalised linear mixed model in the primary analysis in section 4.1 will be re-conducted with each of these replacements to the outcome.

3) Some patients might have missing data for the 'living at home' at 6 months outcome due to missing place of assessment and/or death status. Patients with missing 'living at home' at 6 months outcome will have their missing place of assessment and/or missing death status imputed using multiple imputation (MI). A fully inclusive MI will be conducted with; gender, age, education, place of baseline assessment, if consent signed by 'consultee', and other factors expected to relate to the main outcome (i.e. practice, presenting problems at baseline, diagnosis of delirium at baseline) as covariates. The primary outcome will then be re-derived using the same method as in section 2.1.1. The generalised linear mixed model in the primary analysis in section 4.1 will be repeated for the imputed dataset and the results compared to those from the primary analysis.

4) This sensitivity analysis will only be conducted when the 12 month follow-up data is available. The generalised linear mixed model in the primary analysis (see section 4.1) will be re-conducted with both the 'living at home' data at 6 months and 12 months as the outcome. The model will contain an additional fixed effects for the interaction between randomised group and time, so the treatment

effects and 95% CI can be obtain at each time point, along with the p-value. The model will include a random intercept for each patient to account for the repeated measures on the same patient. This will not be reported in the main analysis report, this will be reported in the additional statistical report containing the 12 month outcomes.

7 SUBGROUP ANALYSES

1) A planned subgroup analysis will be conducted to test the effect of cognitive impairment (MoCA positive) on delirium (CAM positive) at 6 months only. This analysis should be considered exploratory. A subgroup effect will be investigated through fitting an interaction term for cognitive impairment and randomised group into a generalised linear mixed model with delirium at 6 months as the outcome. The model will include the interaction term for cognitive impairment and randomised group, gender, known cognitive decline, and baseline delirium as fixed effects, and centre as a random effect. The results for the subgroup analysis will be reported in a forest plot, along with the overall intervention effect. In addition to the effect size and 95% CI for the intervention effect in each level of the subgroup, the p value for the interaction term will be reported.

8 ADDITIONAL EXPLORATORY ANALYSIS

The following analysis has been planned as exploratory only.

1) Charlson Comorbidity index

The Charlson index [6] assesses whether a patient will live long enough to benefit from a specific screening measure or medical intervention. The Charlson index is used to derive a variable for Charlson score and Charlson probability, and is assessed by baseline and 6 months follow-up. The Charlson index is a 16 item questionnaire (variables *ccicon1 – ccicon16*) with questions on if the patient has a particular comorbidity or not. To obtain the Charlson Comorbidity Index score add up the score from each question in the index, add an extra point if the patient is aged between 50 and 59, add 2 extra points if the patient is aged between 60 and 69, add 3 extra points if the patient is aged between 70 and 79, add 4 extra points if the patient is 80+, and add 0 extra points of the patient is less than 50. To obtain Charlson probability (10-year survival):

$$Charlson\ probability = 0.983^{e^{CII*0.9}}$$

Where CII = Charlson Comorbidity Index score.

The mean, standard deviation, median, minimum value, and maximum value of the Charlson comorbidity score and Charlson probability will be presented at each time point and in each randomised group. No statistical tests for differences will be performed.

2) Clinical Diagnosis of Delirium at Baseline

Delirium is measured at baseline, 3 days, 5 days, and 1 month follow-up using the CAM questionnaire. A clinical diagnosis of delirium is also collected at baseline. The frequencies and percentages of patients that have a clinical diagnosis of delirium at baseline will be summarised in a two-way table against the frequencies and percentage of patients that were tested positive for delirium by the CAM questionnaire. This is exploratory only to see how these two methods compare. No formal analysis will be conducted.

9 SAFETY ANALYSIS

All patients randomised will be included in the safety analysis.

All serious adverse events (SAE) occurring during the trial enrolment period shall be detailed and reported by randomised group. The overall incidence of patients experiencing at least one SAE will be compared between the randomised groups using a chi-squared test and the difference in proportions with 95% confidence intervals will be presented. Where a patient reports more than one of the same type of event, separate tables will be presented showing a) counts of events and b) counts of patients experiencing at least one type of this event.

9.1 ADVERSE EVENTS

The potential risks to patients of the research may include a fall (either in the HAH setting or inpatient setting), hospital acquired infection for patients randomised to inpatient admission, hospital admission for those randomised to HAH, post-discharge hospitalisation and death for all patients. All SAEs occurring during the study, either observed by the recruiting clinician or reported by the patient, will be recorded on the AE Log CRF and SAE Log CRF. All SAEs will be recorded whether or not attributed to the HAH with CGA intervention. All SAEs will be forwarded by the site to the PC-CTU and the trial manager, using the "PC-CTU SAE Report Form" following assessment for seriousness by the site clinician. Adverse events will be summarised descriptively according to randomised group, no statistical comparison will be undertaken on this data.

10 VALIDATION

At a minimum the primary analysis ('living at home' at 6 months), sensitivity analysis, and safety analysis in the main statistical analysis report will be validated. The primary outcome for the secondary analysis ('living at home' at 12 months) will also be validated when available. Validation will be conducted by a trial statistician who has not performed the main analysis or authored the SAP.

11 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

The primary outcome in the published protocol was originally planned to include data collected at both the 6 and 12 months' time point. However, it was decided to analyse the data collected at the two time points separately because it is now planned to potentially publish the results from the 6 months analysis before the 12 month follow-up is complete. All data that is collected at the 12 months' time point will be analysed separately from the 6 months data. In terms of the primary outcome, the analysis of both the 6 and 12 month data will be conducted as a sensitivity analysis.

The statistical analysis methods section in the publish protocol states that the primary outcome of 'living at home' and other binary outcomes will be analysed using a mixed-effect logistic regression model. It has been decided to analyse the binary outcome by means of a generalised linear mixed model instead so that relative risk measures can be obtained from the model.

12 REFERENCES

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13 APPENDICES

Appendix I. Schedule of study procedures

Procedures	Visit					
	Baseline	**3 days**	**5 days**	**1 month**	**6 months**	**12 months**
Informed consent	X					
Eligibility assessment	X	X	X		X	X
Randomisation	X					
Demographics	X					
Medical history	X					
Physical examination (where judged clinically appropriate)	X					
Trial specific questionnaires	X[123]	X[2]	X[2]	X[2]	X[3]	
Health resource questionnaire	X				X	
Patient feedback questionnaire				X		
Adverse event assessment		X	X		X	X

[1] Short form of the informant questionnaire on cognitive decline in the elderly measured at baseline only

[2] Confusion assessment method measured at baseline, 3 days, 5 days, and 1 month only.

[3] Barthel index of activities of daily living, Charlson comorbidity index, Montreal cognitive assessment and EQ-5D-5L measured at baseline and 6 months only.

Appendix II. Outcome assessment schedule

Outcomes	**Visits**					
	Baseline	**3 days**	**5 days**	**1 month**	**6 months**	**12 months**
Demographics	X					
Medical history	X					
Barthel index of activities of daily living (Barthel)	X				X	
Confusion assessment method (CAM)	X	X	X	X		
Charlson comorbidity index	X				X	
Health resource questionnaire	X				X	
Short form of the informant questionnaire on cognitive decline in the elderly (IQCODE short)	X					
Montreal cognitive assessment (MOCA)	X				X	
EQ-5D-5L (UK English)	X				X	
Adverse event assessments		X	X		X	X
Collection of mortality/living at home	X	X	X	X	X	X

Appendix III. Questionnaire scoring

Questionnaire	Possible range of scores	Higher or lower score indicates better health
Charlson Index (Comorbidity)	0-36	Lower
Barthel Index (Activities of daily living)	0-20	Higher
MOCA (Cognitive impairment)	0-30	Higher ≥26 is considered normal (≥18 is considered normal if visually impaired)
IQCODE short (background cognitive status)	1-5 (mean score across all questions)	Lower (3 indicates not much change in last 10 years)
EQ5D VAS (Health status)	0-100	Higher

Appendix IV. Flow diagram of trial participants