Research Ethics Committee Ref (England, Wales & Northern Ireland): 14/WA/1081
Research Ethics Committee Ref (Scotland): 14/SS/1046

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'

Internal Reference Number / Short title: Randomised Controlled Trial (RCT) of Comprehensive Geriatric Assessment (CGA) in a Hospital at Home (HAH) setting

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Date: 11/05/2017 **Version:** 4

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Sponsor: University of Oxford

Funder: NIHR Health Services Research and Delivery programme

Chief Investigator Signature:

No potential conflict of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1. SYNOPSIS

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'	
Internal ref. no. / short title	Randomised Controlled Trial of Comprehensive Geriatric Assessment in a Hospital at Home (HAH) setting	
Study Design	Randomised Controlled Study	
Study Participants	Older people, aged ≥65 years, with markers of frailty or prior dependence who have been referred to admission avoidance hospital at home service 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.	
Planned Sample Size	1552 Participants	
Planned Study Period	4 years and 6 months with participation duration of 12 months.	
	Objectives	**Outcome measures**
Primary	To test the effectiveness and cost-effectiveness of admission avoidance HAH with CGA compared with hospital admission with CGA .	'Living at home' (the inverse of death or living in a residential care setting) at 6 months. Secondary endpoints for the primary objective: incidence of delirium, mortality, new long-term residential care, cognitive impairment, activities of daily living, quality of life and quality adjusted survival, length of stay, readmission or transfer to hospital, resource use (health and social care and informal care), costs and cost-effectiveness. Follow-up times: 6 months for mortality, new long-term residential care, cognitive impairment, activities of daily living, quality of life and quality adjusted survival, length of stay, readmission or transfer to hospital, resource use (health and social care and informal care), costs and cost-effectiveness. 12 months for living at home; (we may follow up with each patient's GP to mid-2017 to collect information on admission to hospital and death).

Secondary	To conduct a process evaluation to describe the setting in which HAH is delivered and how this differs from inpatient care.	How the delivery of CGA in a home setting differs from the interventions described in the Cochrane Review; how a change in national and local policy might impact on the way CGA is delivered in a HAH and inpatient setting.
	To conduct an interview study to explore the experiences of patients and carers.	The process of care and relatives/caregivers perceptions and experience of HAH and inpatient care respectively, this will include information received, practical and social support.

2. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
CGA	Comprehensive Geriatric Assessment
DMC/DMSC	Data Monitoring Committee/ Data Monitoring and Safety Committee
EMU	Elderly Medical assessment Unit
GCP	Good Clinical Practice
GP	General Practitioner
HaH	Hospital at Home
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
NHS	National Health Service
NRES	National Research Ethics Service
PC-CTU	Primary Care Clinical Trials Unit
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee

SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File

3. BACKGROUND AND RATIONALE

Older people are being admitted to hospital as an emergency in increasing numbers. From a system perspective this trend is not sustainable, and from a patient perspective there are many reasons to question whether a hospital is the best place of care for older adults with frailty. There is some evidence that indicates hospital care can be potentially harmful due to a lack of mobility and a risk of hospital acquired infection. A growing evidence base has suggested that organising acute hospital care for older people along the lines of Comprehensive Geriatric Assessment (CGA) is safer than care in a general medical setting. However, the current economic climate does not allow for the expansion of hospital bed numbers to match the growth in admission numbers.[3; 4] There is also concern about the suitability of the hospital environment for older people with complex health care problems who are often in need of some form of rehabilitation, and for whom the process of recovery is likely to be multi-dimensional, recursive and prolonged. The high cost of hospital based care is also a major driver to innovate. There is a need to explore whether CGA in a HAH setting, a care model that is being rolled out across the NHS as hospitals deal with the rise in emergency admissions, results in improved patient outcomes and cost-effective care. A key question is how effective and cost effective it is to deliver CGA in an admission avoidance HAH setting, compared with delivering CGA in an inpatient setting. There is potential that implementing CGA in an older person's home, instead of in an acute hospital setting, will lead to a greater improvement in health outcomes at lower cost.

The intervention
The intervention is admission avoidance HAH with CGA.

Admission avoidance HAH
Admission avoidance hospital at home with CGA provides co-ordinated, multi-disciplinary and integrated care in the home for people who would otherwise be admitted to hospital. Admission avoidance HAH services provide care seven days a week for patients; admissions are restricted to Monday to Friday, 0900 to 1800hrs, although emergency medical cover is available 24 hours a day if needed. All the schemes admit patients with multiple diagnoses who have had an acute change in their health or functional status. Admission avoidance HAH with CGA will be led by geriatric specialist medical staff working with a multi-disciplinary team comprised of nursing staff experienced in geriatric care, allied health professionals (at a minimum a physiotherapist and occupational therapy) and access to specialised psychiatric care, social workers, speech and language therapy, dieticians and pharmacy support. Specialist trainees and suitably qualified healthcare professionals may also provide healthcare and patients will be able to access care from GPs and the primary healthcare team as usual; and inpatient care if required. The core features of the intervention (admission avoidance HAH with CGA) are:

<u>Staff:</u>
- Specialist Geriatric medical staff
- Multidisciplinary team (MDT) care by nurses, physiotherapists, occupational therapists and social workers (this may be part of the primary health care team or dedicated staff)

- MDT meetings with authority to implement recommendations, refer to other services (e.g., older peoples' mental health services, social workers)
- Access to GP and primary healthcare team
- Access to social workers, dieticians, speech and language therapy, mental health services and pharmacy support on referral
- Access to diagnostic services on referral
- Access to inpatient care if referred

Process features

- Mechanism of referral i.e., direct referral from GP, via Rapid Assessment Unit or a Bed Bureau
- Access to inpatient hospital care if required
- Standardised assessment tools for multiple domains such as cognition and activities of daily living
- Rehabilitation plans including discharge planning
- Follow up where appropriate by relevant agencies (e.g., outpatient follow up on discharge)

Desirable features

- Ability to manage patients requiring intravenous infusions, administration of medication via a pump.
- 24 hour care available if required

Comprehensive Geriatric Assessment

CGA was developed in response to concern that problems experienced by older people who required acute hospital level care were not being recognised and acted on.[1] CGA is a multidimensional interdisciplinary diagnostic process focused on determining a frail older person's medical, psychological and functional capability to ensure that problems are identified, quantified and managed appropriately.[2] The multidisciplinary team includes, at a minimum, specialist medical, nursing and physiotherapy and occupational therapy staff. Members of the multidisciplinary team are responsible for delivering the recommended treatment or rehabilitation plan (such as physiotherapy input or occupational therapy, diagnostics or medical treatment).

Control group intervention

Patients recruited to the trial who are randomised to inpatient care will receive their care by a specialist led geriatric service (CGA). We anticipate that the majority will receive care in a specialist ward (estimated to be approximately 80%). The remaining 20% may receive CGA in a general medical ward. This variation will reflect the challenges of real-life systems and continued pressure on beds. Measures, in the form of participating centres agreeing protocols, have been taken to ensure that the features of usual care are comparable and consistent with the evidence for inpatient CGA.

Summary of findings of relevant clinical trials

The evidence for admission avoidance HAH, which is co-ordinated multi-disciplinary acute care in a home setting for patients who would otherwise require hospital admission, is from a Cochrane Review (N=10 RCTs recruiting 1327 patients).[5] Although a statistically significantly lower mortality was observed for those whose admission to hospital was avoided at 6 months follow-up (HR 0.62, 95% CI 0.45 to 0.87 N=607), there remains some uncertainty around the effectiveness and cost-effectiveness of this form of care as part of a wider Acute Care strategy. Only three small trials contributed to this meta-analysis and the comparison was inpatient care without CGA. Therefore a number of important questions are left unanswered, including the effectiveness of admission avoidance CGA compared with inpatient CGA. A further concern is that this result may be a chance finding and that the risk of publication bias cannot be ruled out.

A second potential benefit from delivering CGA in a hospital at home setting is a reduction in delirium for

patients allocated to admission avoidance HAH. Delirium, an acute confusional state, is a frequent and serious complication in older people who develop an acute illness. It is characterised by disturbed consciousness and changes in cognitive function and / or perception that develop over a short period of time. It is associated with adverse consequences, which include increased risk of hospital-acquired complications, new admission to institutional care, new dementia, increased hospital length of stay and increased mortality. There is preliminary evidence that care for older people in the less stressful environment of their own home is associated with a reduced incidence of delirium.[6;7] If the benefit of a reduced incidence of delirium was confirmed by the results of this RCT there will be significant implications for vulnerable patients with reduced functional and cognitive decline or admission to residential care. This may have additional economic benefits.

Summary of known and potential risks and benefits to participants
The intervention, admission avoidance HAH with CGA, is an established service in each of the recruiting centres. We will adhere to current arrangements for clinical practice and patients will be transferred to hospital if they require access to acute inpatient facilities. Patients will be able to access care from GPs and the primary healthcare team as usual; and inpatient care if required. The potential risks to participants 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 participants. We will recruit participants with cognitive impairment and it is possible that the burden of completing data collection may be particularly onerous in this patient group. Potential benefits to participants include monitoring of health status and an opportunity to comment on healthcare received due to involvement in a research study.

Description of population to be studied
We will recruit older people with frailty and who are the target population for HaH services. Older adults with frailty often present with non-specific presentations, acute functional deterioration, delirium, falls and complex comorbidity, sometimes referred to as acute geriatric syndromes.[8] Often these acute crises precipitate an acute hospital admission. There is no simple accepted definition of this population due to variation in the acute presenting illness. However, it is agreed that the degree of prior disability is important and that attempts to define this group should be problem based.[9] We will describe patients recruited to this trial according to functional dependence, cognitive impairment, comorbidity, history and/or presence of delirium and presenting complaint (such as falls, reduced mobility, confusion, carer strain). The inclusion of patients with cognitive impairment or dementia is necessary to ensure the study sample represent the patients requiring these services.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	Outcome Measures/Endpoints
Primary Objective To test the effectiveness and cost-effectiveness of admission avoidance 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.	Primary: 'living at home' (the inverse of death or living in a residential care setting) at 6 months. Secondary outcomes for the primary objective: incidence of delirium, mortality, new long-term residential care, cognitive impairment, activities of daily living, quality of life and quality adjusted survival, length of stay, readmission or transfer

	to hospital, resource use (health and social care perspective and also costs of informal care), costs and cost-effectiveness. 'Living at home' (the inverse of death or living in a residential care setting) at 12 months Follow-up times: 6 and 12 months; (we may follow up with each patient's GP to mid-2017 to collect information on admission to hospital and death).
Secondary Objectives: To conduct a process evaluation to describe the setting in which HAH is delivered and how this differs from inpatient care.	How the delivery of CGA in a home setting differs from the interventions described in the Cochrane Review; how a change in national and local policy might impact on the way CGA is delivered in a HAH and inpatient setting.
To conduct an interview study to explore the experiences of patients and carers.	The process of care and relatives/caregivers perceptions and experience of HAH and inpatient care respectively, this will include information received, practical and social support.

5. STUDY DESIGN

A multi-site unblinded randomised controlled trial with a process evaluation and an interview study. Participants will be part of the study for 12 months after enrolment and randomisation.

Data collection

Data will be collected from participants, and from their caregivers if the caregiver is the designated consultee, by a suitably qualified member of the research team at baseline, six and 12 months, after randomisation, either in the participant's home or an alternative setting (hospital or residential care). We will limit the collection of data at twelve months to the primary end point. Standardised and validated questionnaires will be used to collect data on functional ability, quality of life and satisfaction; resource data will be collected from participant's GP records by the research nurses and by the participants completing a diary. In addition we will assess patients for delirium at 3 and 5 days, and again at 1 month after recruitment. We have opted for members of the research team to collect this data to reduce respondent burden in this frail and older population. The member of the research team who collects data will enter patients' responses to structured and validated questionnaires to an electronic pro forma; they will also carry paper copies of the questionnaire as a back-up.

5.1. Interview Study

Approximately six patients and their carers per selected site (until data saturation), from a HAH setting and from an inpatient setting, will be selected from the patients randomised to HAH or inpatient admission from a sample of the recruiting sites. These patients and their carers will be invited to be interviewed by a suitably qualified researcher at the point of discharge or immediately after discharge

from their care setting. Patients and carers will be selected to include those with cognitive impairment, those who are physically frail and who have experienced varied types of health crises (sudden onset of chronic illness, deterioration in the context of multiple health problems and acute exacerbation of a chronic condition) that will impact on the recovery process. We will seek guidance from healthcare staff and relatives on the appropriate time to conduct the interview. The interviews will assess the process of care and how the healthcare they received facilitated recovery, as well as relatives/caregivers perceptions and experience of HAH and inpatient care. Interviews will be recorded by the qualified researcher.

A trained researcher will complete a structured pro-forma to record the key features of the HAH with CGA intervention and of inpatient care, this will include the use of care protocols, the method of assessing the patient, and conversations with the staff delivering the intervention

Flowchart (see appendix A)

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

We will recruit older people (aged ≥65 years) with frailty and an acute health crisis. These types of patients typically present with non-specific presentations, acute functional deterioration, delirium, falls and complex comorbidity, sometimes referred to as acute geriatric syndromes. We will include people with cognitive impairment as a component of frailty.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for 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 has 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.

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patient 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 presenting with a suspected stroke.
- Patients who are receiving end of life care as part of a palliative care pathway.
- Patients who refuse the 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 would not be acceptable (in keeping with existing clinical practices for HAH).
- Patients living in a residential setting.

7. STUDY PROCEDURES

See Appendix

7.1. Recruitment

We have discussed and agreed with the clinical leads from each centre a method of recruitment that will cause minimum disruption to existing services by fitting in with existing referral arrangements. A suitably qualified member of the research team in each centre will be based at the referral centre and will carry a mobile phone for contact by the clinical lead if a potentially eligible patient has been referred and they are off site collecting follow-up data. Patients can be admitted to admission avoidance HAH with CGA services from Monday to Friday during office hours. Two broadly similar referral systems operate, and are usual care in these settings:

i) GPs refer by phone older people to community clinical leads, who may be geriatricians or community matrons. The clinical lead for HAH will discuss each patient referral with a consultant geriatrician. In at least one centre calls are routed through a bed bureau. Each patient is usually assessed in approximately two hours and then triaged on clinical grounds to inpatient care or admission avoidance HAH. Patients deemed too acutely unstable (who will be excluded from participating in the trial) may be admitted to hospital at this point. If triaged to admission avoidance HAH, and eligible for admission avoidance HAH, the clinician will raise the possibility to the patient of participating in this RCT. At this point the research nurse, or suitably qualified equivalent, will be contacted about potentially eligible patients.
ii) Acutely ill older people are seen daily in an Elderly Medical Assessment Unit (EMU) following referral from GPs and A&E (over 7,000 patients per year). Eligible patients will be identified by consultant geriatricians for referral to the admission avoidance HAH with CGA service. The research nurse, or suitably qualified equivalent, will be contacted by clinical staff in the EMU about potentially eligible patients.

In some centres the research nurse role will be shared with clinical duties enabling the research nurses to respond to new calls and potentially recruit eligible patients. It is anticipated that patients will have approximately two hours to decide if to participate in the study; this will fit with current arrangements for referral and admission.

7.2. Informed Consent

At the point of referral to inpatient care or admission avoidance HAH a suitably qualified member of the research team will provide each eligible patient and their carer, if they have one, with written and verbal Participant Information describing the research and give them an opportunity to discuss their questions and concerns about the research. Following this discussion the patient will be asked if they are interested in participating in the trial. The written information, in the form of a Patient Information Leaflet, will describe in detail the nature of the study (research question, study design and outcomes), what it will involve for the participant and the known risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

This study will include adult participants with cognitive impairment/dementia who are unable to consent for themselves. We think this is necessary because, if recruitment is restricted to patients with capacity, such a restriction would lead to an unrepresentative study sample. The consent process will therefore take into account the implications of the Mental Capacity Act (2005) in England, Wales and Northern Ireland and the Adults with Incapacity Act (2000) in Scotland. A relative, friend or Independent Mental Capacity Advocate will be involved in making a decision in the best interests of individuals if they do not have capacity to give consent. If necessary this consultee consent will be taken verbally over the phone and the paperwork sent to the consultee to be signed to record the consent. We will reassess capacity at each follow-up visit and re-consent a participant if their capacity changes between baseline and follow-up at six and twelve months. Participants, or their representatives, will be asked to sign and date the

latest approved version of the Informed Consent form before any trial specific procedures are performed.

It is anticipated that consent and randomisation will usually take approximately two hours to fit with current arrangements for referral and admission of patients to HAH or acute hospital, as such it will be similar to other hyper-acute studies. All participants will be given the opportunity to question the Investigator, the geriatrician lead or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the suitably qualified member of the research team who presented and obtained the Informed Consent, and who will have received training according to the principles of Good Clinical Practice, which will take into account the Mental Capacity Act (2005) in England and Wales and the Adults with Incapacity Act (2000) in Scotland. If the patient has difficulty completing the consent form due to visual impairment or frailty, but is capable of informed consent, a witness signature will be sought from a next of kin or medical professional not working within the trial team to confirm the consent process was appropriately performed.

A copy of the signed Informed Consent will be given to the participant, the clinical lead at the study site and the original signed form will be retained by the member of the research team and stored in a secure office at the participating site. We will seek permission from patients who decline to participate in the study to look at their medical records for clinical information about their health problem.

7.3. Screening and Eligibility Assessment

A speciality physician in geriatric medicine, or a suitably qualified health professional, who works at the interface of the hospital and admission avoidance HAH will refer participants who are eligible for both admission avoidance HAH and hospital admission to a senior clinician in each research site. All patients are routinely screened by a suitably qualified healthcare professional for their suitability for HAH. Pulse, blood pressure, temperature, respiratory rate and other physiological components of assessment are routinely collected, together with clinical history. In addition assessments such as ECG, bloods and urine analysis may be done. Initial assessments focus on the stability of the clinical condition of the patient. These data may be used to inform the eligibility of the patient and will not be collected by the research team.

The clinical lead, or suitably qualified health professional, will discuss with each eligible patient the possibility of participating in this RCT; if the patient is interested the clinical lead will contact a suitably qualified member of the local research team. Based on current procedures we anticipate there will be approximately two hours between a patient being referred to the study and randomisation.

7.4. Randomisation, blinding and code-breaking

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 Trials Unit's in-house online randomisation system. It supports multiple studies and sites, a range of randomisation algorithms (simple, block, stratified and minimised), unbalanced allocation ratios, blind or open trials, email notifications and site package statistics (for blind trials). It is secure, provides full audit logs and has been validated at algorithm and interface levels. Randomisation will be stratified by centre, 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 these two settings. This has been taken into account in our analysis plan and will not affect the estimated precision of our findings. The success of randomisation will be measured by the number declining to be randomised or withdrawing immediately after randomisation. We will monitor this from the start of the study on a daily basis and respond immediately with vigorous, viable plans if we fall behind.

All lead clinicians for each centre are co-applicants and will have an integral role in the running of the study; this will include identifying patients who might be eligible for the study and, together with the research nurse, describing the process of randomisation. It will 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).

We will establish a Data Monitoring Committee (DMC) which will include an independent Chair, an independent trialist and an expert in the care of older people. We will nominate to NIHR HS&DR the names of an independent Chair and members of the committee. The Data Monitoring Committee will meet twice a year as a minimum. Breaking the randomisation code will not be necessary as this is an unblinded RCT.

7.5. Baseline Assessments

Following the completion of informed consent a suitably qualified member of the research team will collect the core baseline clinical data to characterise the study population:

- the presenting problem requiring admission to hospital and age, information will be collected from the patient's clinical notes and/or the clinical lead
- education, will be collected directly from the patient or their caregiver
- prior level of functioning and attainment, will be assessed from the patient's clinical notes and/or the clinical lead
- Background cognitive status measured by the IQCODE, a 16 item informant based questionnaire, which can also be completed by a carer and takes 5 minutes to complete. This questionnaire assesses previous cognitive decline by measuring change in aspects of cognitive function and behaviour rather than current function.[13]
- sensory impairment, collected from the patient's clinical notes and/or clinical lead
- psychiatric illness and physical or neurological problems will be collected from the patient's clinical notes and/or clinical lead
- incident and persistent delirium
- any other baseline information deemed appropriate by the research team for the patient's participation in the trial

The following baseline data for measures of outcome will be collected by a suitably qualified member of the research team once the patient has been admitted to HAH or inpatient care:

- Co-morbidity measured by the Charlson Index.[10]
- Activities of daily living measured by the Barthel Index.[11]
- Current cognitive impairment measured by the MOCA.[12]
- Incident and persistent delirium measured by the Confusion Assessment Method (CAM).[14]
- Health status measured by the EQ5D.[15]
- Major health service use (for example admission to hospital) in the year prior to their current illness, this data will be obtained directly from the patient and/ or their carer.

If the patient appears to be burdened by the collection of baseline data we will use a two stage approach, with core data collected prior to randomisation and following consent, and the remaining data collected soon after randomisation.

7.6. Subsequent Visits

Patients recruited to the trial will be assessed for all outcome measures, except delirium, a total of two times: i) at baseline (prior to randomisation), and at ii) 6 months; the secondary end point 'living at home at 12 months' only will be collected at 12 months. We will assess patients for delirium at 3 and 5 days (to assess incident delirium) and at 1 month (for persistent delirium). Data on living at home, admission to hospital, mortality, adverse events while in hospital or HAH and admission to residential care will be collected from patients, from their hospital notes and from their GP records at six month follow up and the primary end point only at twelve month follow-up. Patients will be assessed and data collected directly from the participants in their home or other residential setting. If appropriate we will assess patients for delirium, using the Confusion Assessment Method, by telephone. If this isn't possible we will conduct a face to face assessment.

We will interview a small sample of patients and carers (approximately six patients and their carers from a sample of the recruiting sites) close to the time of discharge from HAH or hospital.

7.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the investigator at each site may discontinue a participant from the study at any time if he/she considers it is necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).
- Significant protocol deviation.
- Withdrawal of Consent.
- Loss to follow up.

If given, the reason for withdrawal will be recorded in the CRF.

Participants randomised and admitted to admission avoidance HAH with CGA or inpatient admission will be admitted on average for 14 days. If a participant withdraws from the study we will recruit an additional patient, providing this does not extend the duration of the study. We will only exclude data from a participant who has withdrawn from the study if they request we do so.

7.8. Definition of End of Study

The end of the study will be the date of the last visit or telephone follow-up to collect data from a participant by a member of the research team.

8. SAFETY REPORTING

8.1. Definition of Serious Adverse Events

The potential risks to participants 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 participants.

An adverse event will be deemed serious if it:

- Results in Death
- Is life threatening*
- Requires hospitalization or prolongation of existing inpatient hospitalization
- Results in persistent or significant disability or incapacity
- Is an important medical event

*Life threatening in this case refers to an event where the subject was at risk of death at the time of the event and does not refer to an event which hypothetically might have caused death if it was more severe.

It is important to note that because death is one of the outcome measures in this trial deaths will be collected on a Death form within the CRF and not on an SAE form. Expectedness and Relatedness will also be captured on the death form.

Expected events for this patient population include:

- Falls
- Pressure Sores
- Hospital or community acquired infection
- Transfer to hospital

8.2. Reporting Procedures for Serious Adverse Events

All SAEs which are related to administration of any of the research procedures, and are an unexpected occurrence, either observed by the recruiting clinician or reported by the participant, will be recorded on the CRF, , and forwarded by the site to Nuffield Department of Population Health Clinical Trials Service Unit (CTSU) and the trial manager following assessment for seriousness by the site clinician,

Then the “PC-CTU SAE Report Form” will be completed. As a minimum, the following information will be recorded:

- Description
- Date of onset
- End date
- Assessment of relatedness to the HAH with CGA intervention
- Other attribution/co-intervention
- Action taken.

Follow-up information will be provided as necessary.

SAEs will be reported within 24 hours of the PI being notified of the event.

The CI or delegate will report SAEs, which in the opinion of one of the Clinical Leads (Dr Graham Ellis or another suitably qualified Doctor who is involved with the trial) are 'related' and 'unexpected' when relating to the study procedures, to the REC within 15 working days of the CI becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

Following the initial check of the report, any additional information will be requested, and the CI or their medically qualified designated representative will review and evaluate the report for seriousness, causality and expectedness in a timely manner. If the clinical lead disagrees with the assessments of causality made by the sites PI, the site PI's assessment cannot be downgraded. Where there is a discrepancy the worst case assessment is used for reporting purposes. Digital confirmation and sign off of the SAE form as an email may be utilised to obtain PI review and signature.

The SAE reports will also be reviewed by the Data Monitoring Committee (DMC), at least twice during the study at face-to-face meetings.

Additional information, as it becomes available, will also be reported on the SAE Report Form (i.e. updating the original form). The SAE Report Form will be filed in the Trial Master File according to PC-CTU SOP TM12 'Trial Master File', with copies filed in the Case Record Form file and the Investigator Site File.

Trial Manager will complete regular reports reviewed by the senior members of the Trial Steering Committee (TSC) and the DMC. One of the metrics contained within this reporting is the number of SAEs reported and the cumulative number of SAEs for each study. Any concerns identified will be immediately raised with the Chief Investigator and may be tabled for discussion at DMC. The DMC also monitors the frequency and pattern of events reported as part of its independent oversight of the trial.

9. STATISTICS AND ANALYSIS

9.1. Description of Statistical Methods

All analyses will be intention to treat (effectiveness) and based on a mixed effect model with the intervention arm as patient level fixed effect, as these models allow adjustment for recruitment centre (random effects) and individual patient characteristics. For the primary outcome of living at home six months, the primary analysis will use a generalisation of the logistic model to mixed effect models. We will assess the impact of missing data on the primary analysis by carrying out sensitivity analyses based on imputing (multiple imputation) the missing values. Similar models will be used for all binary outcomes (presence of delirium, cognitive impairment, etc). Equivalent models for continuous outcomes (e.g. normal distribution) will be used for the Barthel score. We expect length of stay to be highly skewed so other parametric models might be required for this and in case of poor fit simple non-parametric tests (non-adjusted) will be used instead for this outcome. We have planned one sub group analysis of the effect of care setting (home vs. hospital) on the incidence of delirium in people who are cognitively impaired (defined by the MOCA). Delirium will be measured by the Confusion Assessment Method (CAMS).

9.2. The Number of Participants

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 1/3rd 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, 607participants) 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% [37] 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 to achieve 90% power at a significance level of 0.05, we will need to recruit 1350 participants to detect a 10% absolute difference, assuming a control group event rate at 12 months of 50%. The estimated recruitment rate allows 15% attrition resulting in a projected sample size of 1552. We have re-examined the sample size calculation using an estimate of the intra-cluster correlation (ICC) of 0.005, this would provide 88% power to detect the assumed effect size of RR=80%, for a two tailed alpha of 0.05.

9.3. Analysis of Outcome Measures/Endpoints

Economic analysis

The costs in each arm of the study will be calculated on an intention to treat basis, and will be reported from a health care and a health and social care perspective; in addition the informal care will be separately quantified and valued. Quality-adjusted life years will be derived from EQ-5D responses valued using the UK "tariff", using linear interpolation between baseline and six month values and adjusting for within-trial mortality. Resource use information will be collected on health and social care services used, including preparation and delivery of the interventions, hospital in-patient stays and procedures, out-patient and day-case use, hospital at home durations, other consultations (including GP and community nurse consultations), medications, adverse events, admission to respite care and long term care and use of other social care. Data on GP and nurse consultations will be collected from each GP practice by the research nurses for each centre. We will also collect this data using additional short simple questionnaires at the 6 month follow-up to capture information on resource use, out of pocket costs and informal care time. Resource use volumes will be multiplied by appropriate national unit costs such as NHS Reference Costs to derive a cost per participant.

The main cost-effectiveness measure will be the estimated net cost per quality adjusted life year gained, for the within-trial period. In the event of a within-trial difference in mortality, average life expectancy will be estimated for trial recruits using information from life tables and relevant cohort studies, and used to estimate quality adjusted life years gained/lost. Uncertainty concerning the reported cost-effectiveness ratio will be handled using the non-parametric bootstrap and reported using cost-effectiveness acceptability curves, scatters on the cost-effectiveness plane, and 95% confidence intervals (using the percentile method) around the net benefit statistic. In addition, sensitivity/scenario analyses will be conducted for different cost perspectives: these will include analyses in which the costs of admission avoidance HAH with CGA and in-patient CGA are allowed to vary across a range observed in the study, and analyses in which informal care costs are excluded or included.

Analysis of contextual data

A narrative, descriptive account of the organization of services at each centre will be produced drawing on data collected from individual centres via the structured pro-forma, an events log (that will include discussions with staff) and formal documents relating to organisation and delivery. This will include a description of the dimensions of admission avoidance HAH and inpatient hospital settings; and any changes to staffing and service organisation that might impact on the delivery of CGA (for example loss/reduction of geriatrician input; ward re-organisation/closures; expansion/contraction of scope of

HAH provision). Through comparison within centres and across service delivery sites, we will develop a typology of admission avoidance HAH with CGA and inpatient CGA as implemented; and develop hypotheses to explore patterns of variation in trial outcomes.

Analysis of qualitative interviews with patients and caregivers

We will use a grounded theory analytic approach in the qualitative study, combining simultaneous data collection and analysis, constant comparison and search for negative cases. The rationale for the adoption of a grounded theory approach to analysis is two-fold. First, the approach is flexible yet systematic and robust through the use of iterative, simultaneous data collection and analysis, constant comparison, search for native cases and memo writing to generate concepts and categories as well as their properties and dimensions through the coding process. A second important feature is a focus on context and process. This approach will provide a more robust, systematic and in-depth approach to addressing issues of context and process, critical in this study. Our coding process will generate elements that can be grouped into concepts and then into higher order categories, which will form the basis of our theory of patients' perception of recovery and the factors contributing to it (e.g., personal and social resources, content and process of service delivery). We will recruit additional respondents based on key features to test out aspects of our developing grounded theory (via theoretical sampling).

10. DATA MANAGEMENT

Source documents are where data are first recorded, and from which participants' CRF* data are obtained. These include, but are not limited to, trial questionnaires, clinical notes, GP and hospital records (from which medical history and previous and concurrent medication and resource use may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All paper documents will be stored safely in confidential conditions, and electronic data in a secure, protected environment. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

The data management will be run in accordance with the PC-CTU SOPs, which are fully compliant with the Data Protection Act and Good Clinical Practice (GCP). Data will be directly entered into laptop computers, paper copies of the questionnaires may also be used to allow double data entry. Interviews will be audio-recorded, fully transcribed and entered into NVivo software. Field notes pertaining to the physical, social and care environment of the home setting will also be managed and analysed. All audio-recordings and field notes will be stored safely in confidential conditions and electronic data in a secure, protected environment.

* The term CRF and eCRF (electronic) are used interchangeably in this paragraph. Direct entry into an eCRF is the preferred method of data capture, but paper copies will be provided as a back-up (alternative).

10.1. Access to Data

Data will be kept in accordance with the Data Protection Act. The Clinical Trials Unit SOPs, which are designed to protect patient confidentiality, will be followed. No-one outside the study team will have access to either the CRFs or the database; members of the research team will be able to access patient

identifiable data in order to collect follow-up data. Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

10.2. Data Recording and Record Keeping

In order to be compliant with Good Clinical Practice (GCP) and regulatory requirements, all key data management activities will be conducted under PC-CTU SOPs and best practices. Information technology SOPs in relation to server installation and maintenance, security, back-up and restoration, system monitoring and user access monitoring, are in place and maintained by the Medical Sciences Division Information Technology team.

All hard copy data will be transferred from the site of the research visits and their local storage location, and consent will explicitly be sought from participants to do so. During the course of the trial study data documents are held securely at the PC-CTU, within access restricted areas. Access to both electronic and paper data is restricted, apart from to relevant study specific staff. Questionnaires, transcripts or electronic audio files, will likewise be held in a locked, protected storage area. These will be transferred from the site of the research visits and their local storage location, and consent will explicitly be sought from participants to do so.

The study database will be securely held and maintained by the PC-CTU. Participant clinical data will be identifiable using a unique trial specific identification number and/or code. Participant identifiers such as names will not be included in any electronic clinical trial data files. Clinical trial data **w**ill be entered by the researcher into an eCRF, and subsequently stored, and managed in a clinical data management system known as OpenClinica. Back-up paper CRFs are offered, and if employed, will be subsequently entered into the same system. OpenClinica supports Good Clinical Practice (GCP), regulatory guidelines such as 21 CFR Part 11, and is built on a modern architecture using leading open standards. The PC-CTU installation has an available system validation package. The study specific instance will be validated using SOPs in relation to database build and programming of data validations. Access to the system will be centrally controlled by a Clinical Data Manager, and will be provided only to personnel who have completed the relevant training. A data management plan (DMP) will be created prior to the first participant enrolment, which will document all data management activities throughout the duration of the trial. On completion of the trial and data cleaning, the study documentation, including patient identifiable information will be transferred to a secure, GCP compliant, external archiving facility, where they will be held according to PC-CTU procedure for a period of 5 years.

11. QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and PC-CTU SOPs. The PC-CTU has in place procedures for assessing risk management for trials which will outline the monitoring required. A monitoring plan using the risk assessment will be produced and both will be reviewed during the study. The monitoring plan will go into details about what level and frequency of monitoring is required. The investigators and all trial related site staff will receive appropriate training in GCP and trial procedures. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents where possible. Following the monitoring plan, the appropriate level of monitoring will take place to verify the clinical trial will be conducted and data generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) will meet twice a year during the recruitment phase of the trial or as indicated by the Chair, and then as determined by the Chair of the TSC and DMC. The DMC will meet prior to the TSC.

Data Monitoring Committee (DMC)

The DMC will report to and advise the Trial Steering Committee who, in turn, will report to and advise the Project Management Group. The DMC will have an independent chair and 'stop rule' authority to advise early termination of the trial in the event of safety concerns or futility from poor recruitment or lack of events. The DMC will convene regularly prior to, during, and following the trial (full description of role see section 10.7). Together, the responsibilities of the committees are:

- To safeguard the safety, rights and well-being of the trial participants.
- To systematically monitor the trial data and review any analysis as outlined in the Statistical Analysis Plan or as requested by the TSC.
- To make recommendations to the TSC as to whether the trial is operating as expected or if there are any ethical or safety reasons why the trial should not continue.
- To consider data emerging from other related studies and its potential impact on the trial, if requested by the TSC.
- To pick up any trends, such as increases in un/expected events, and take appropriate action.
- To seek additional advice or information from investigators where required.
- To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment.
- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

Trial Steering Committee

The TSC will meet prior to recruitment to the trial and at six monthly intervals during recruitment to the trial (or as indicated by the Chair) and then as determined by the Chair. The role of the TSC is to provide overall supervision of the study on behalf of the Project Sponsor and the Funder (NIHR) and to ensure the study is conducted to the standards set out in the Department of Health's Research Governance framework for Health and Social Care and the Guidelines for GCP.

Project Management Group (PMG)

The Project Management Group (PMG) will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The PMG will be comprised of individuals responsible for the trial's day-to-day management (e.g. the CI, clinical lead investigators, trial manager, statistician, data manager) and will meet regularly throughout the course of the trial.

12. ETHICAL AND REGULATORY CONSIDERATIONS

We do not believe that there are any significant ethical issues related to this trial. Site staff will be fully trained in GCP and the trial according to their study role.

It is anticipated that consent and randomisation will usually take approximately two hours to fit with current arrangements for referral and admission of patients to HAH or acute hospital, as such it will be similar to other hyper-acute studies. Following informed consent a suitably qualified member of the research team will collect the core baseline clinical data to characterise the study population and will

collect the remaining baseline data for measures of outcome once the patient has been admitted to HAH or inpatient care.

If the participant lacks capacity to consent we will identify 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. This may be done verbally over the telephone and the consent then recorded by sending the paperwork to the consultee for completion. The consent process will take into account the implications of the Mental Capacity Act (2005) in England, Wales and Northern Ireland and the Adults with Incapacity Act (2000) in Scotland. A relative, friend or Independent Mental Capacity Advocate will be involved in making a decision in the best interests of individuals if they do not have capacity to give consent. We will reassess capacity at each follow-up visit and re-consent a participant if their capacity changes between baseline and follow-up at six and twelve months. Participants will be asked to sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

12.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

12.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

12.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

12.6. Expenses and Benefits

Participants will not be paid.

13. FINANCE AND INSURANCE

13.1. Funding

This study is being funded by NIHR HS&DR.

13.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

14. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. We will disseminate news of our Hospital at Home research through the network of carers groups linked to individual trial centres and through their literature.

15. REFERENCES

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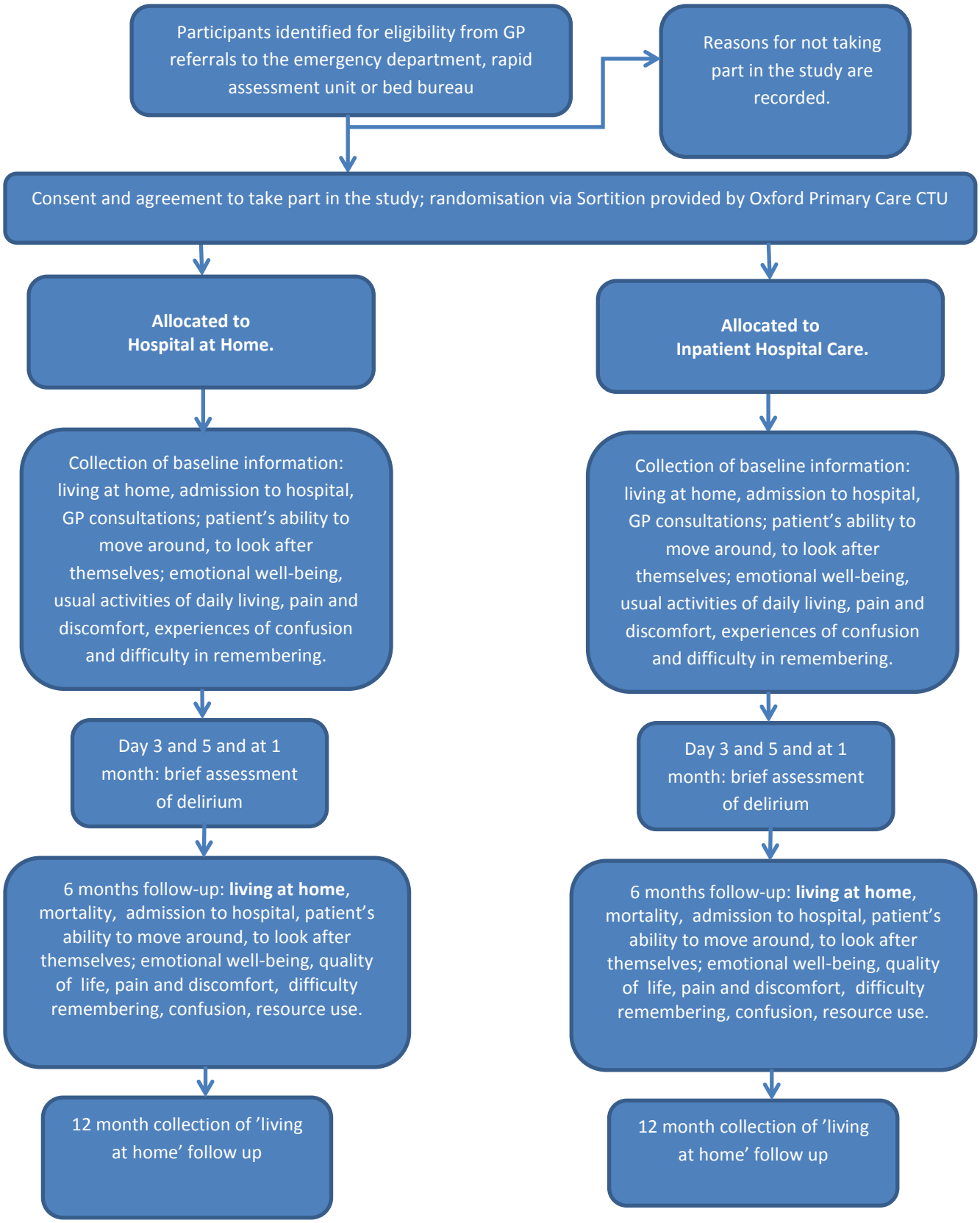
Research Ethics Committee Ref (England, Wales & Northern Ireland): 14/WA/1081
Research Ethics Committee Ref (Scotland): 14/SS/1046

16. APPENDIX A: STUDY FLOW CHART



17. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures		**Visits (insert numbers as appropriate**				
	Screening	**Baseline**	**3 and 5 days**	**1 month**	**6 months**	**12 months**
Informed consent		1				
Demographics		1				
Medical history		1				
Physical examination (where judged clinically appropriate)		1				
Eligibility assessment		1	1		1	1
Randomisation		1				
Questionnaires						
Barthel Index of Activities of Daily Living (Barthel)		1			1	
Confusion Assessment Method (CAM)		1	1	1		
Charlson Comorbidity Index		1			1	
Health Resource Questionnaire		1			1	
Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE short)		1				
Montreal Cognitive Assessment (MOCA)		1			1	
Patient Feedback Questionnaire				1		
EQ-5D-5L (UK English)		1			1	
Adverse event assessments			1		1	1
Collection of mortality/ living at home		1	1	1	1	1

18. APPENDIX C: HISTORY OF AMENDMENTS

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2	30/06/2015	Sasha Shepperd & Andrea Cradduck	Update of all paperwork to reduce burden on patients and correction of typing errors in Protocol & addition of telephone consent
Modified 1	2.1	07/09/2015	Sasha Shepperd & Andrea Cradduck	Scot REC only – Update of all paperwork to reduce burden on patients and correction of typing errors in Protocol
2	2.2	17/09/2015	Sasha Shepperd & Andrea Cradduck	Scot REC only – addition of Telephone consent
3	3	21/12/2015	Sasha Shepperd & Andrea Cradduck	Reduction of 12 month follow up data collection to primary end point only
4	3.1	14/06/2016	Sasha Shepperd & Andrea Cradduck	Addition of Sites in Northern Ireland A substantial Amendment due to the recruitment of subjects lacking capacity.
5	N/A	N/A	N/A	Non-Substantial
6	N/A	N/A	N/A	Non-Substantial
7	4.0	17/03/2017	Sasha Shepperd & Andrea Cradduck	Primary end point to be analysed at 6 months on advice of TSC