Non-CTIMP Study Protocol

Assessing recovery from delirium in older hospitalised people: optimisation and validation of the 4AT.

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Funder	Dunhill Medical Trust
Funding Reference Number	RPGF1902\147
Chief Investigator	Prof Alasdair MacLullich, Professor of Geriatric Medicine
Sponsor number	AC19045
REC Number	Insert REC number before finalisation
Project registration	If applicable trials should be registered on a publicly accessible database. ACCORD can provide log-in credentials for clinicaltrials.gov. Please email resgov@accord.scot to arrange
Version Number and Date	Version 2.0 19 March 2021

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure
DSM-5	Fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders.
4AT	4'A's test
DRS-R98	Delirium Rating Scale-Revised-98

1. INTRODUCTION

1.1 BACKGROUND

Delirium is a severe and distressing neuropsychiatric syndrome which is characterised by acute deterioration in attention and other mental functions. The mental status deterioration develops over short periods of time (usually hours to days) and symptoms tend to fluctuate over the course of the day.[1] Delirium is extremely common: it affects at least 1 in 6 older patients in acute hospitals.[2] Delirium is triggered mainly by acute illnesses, trauma, surgery, or medication. Most cases of delirium last for 2-4 days, though 20% of cases persists for weeks or months.[3] Delirium is independently associated with many adverse effects including patient and carer distress, increased length of stay, a 2-fold risk of death, a 3-fold risk of institutionalisation and an 8-fold risk of new dementia.[4,5] Delirium is also a marker of current dementia and is associated with acceleration of existing dementia.[6,7,8] The economic burden of delirium derived from 2008 US data estimates the one-year health care costs to be $38-$152 billion.[9]

Despite its importance, delirium remains under-diagnosed: more than two-thirds of delirium is missed.[10] Diagnosis of delirium is important to ensure treatment of the presumed medical causes, and management of risk (e.g. falls, hydration) and distress and agitation (e.g. due to hallucinations).[11,12]

Additional to the initial diagnosis, a crucial part of delirium care is determining if the delirium episode has resolved. This is essential to allow clinicians to evaluate the effects of treatments, to manage the risk of complications, and to inform discharge planning. It is also a mandatory part of good practice to inform patients and relatives of the diagnosis and response to treatment. Notably, outcomes (including institutionalisation and mortality) of patients with persistent delirium are especially poor.[13]

Yet there is no clear evidence on what tests clinical staff should use to assess for delirium recovery.[14] The lack of validated methods to assess for recovery of delirium was demonstrated in a comprehensive literature review conducted via the Scottish Intercollegiate Guidelines Network (SIGN) group producing the guidelines on delirium.[12] Delirium assessment tools are mostly designed either to detect prevalent delirium on a single assessment, e.g. the 4AT[15], or for surveillance of non-delirious patients for incident delirium, such as the RADAR (Recognizing Acute Delirium As part of your Routine) scale.[16]

The 4AT (short for the 4 'A's Test) is a brief (<2 min) and practical instrument for delirium detection which is widely implemented in clinical care in the NHS in the UK and internationally. The 4AT has been validated to detect delirium in hospital settings.[17,18] The SIGN guidelines recommend use of the 4AT for detecting delirium in the acute hospital.[12] The 4AT is sometimes used to assess for delirium recovery using repeated administration but it has not been validated for this purpose.

1.2 RATIONALE FOR STUDY

The 4AT is a rapid clinical assessment tool for delirium detection. It is designed to be used by healthcare professionals at their first contact with the patient, or when delirium is suspected. No special training is required, and it is suitable for use in normal clinical practice.

The advantages of the 4AT are that it is:

- quick to administer (2 minutes),
- easy to learn,
- easy to administer and score,
- can be used by professional-level healthcare staff from a variety of disciplines,
- allows scoring of patients who are too drowsy or agitated to undergo cognitive testing or clinical interview,
- takes account of informant history,
- does not require subjective judgements based on interview,
- does not require a quiet environment for administration,
- does not require physical responses such as drawing figures or clocks.

The 4AT is sometimes used to assess for delirium recovery using repeated administration but it has not been validated for this purpose.

The aim of this research study is to validate the 4AT as a tool for assessment of delirium recovery. This is important because it will fill a significant gap in understanding of how clinical staff should monitor delirium symptoms over time and assess for delirium recovery.

Given the high prevalence of delirium and the clear need for a method for assessing recovery, the findings from the present project have the potential for considerable and rapid clinical impact.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective is to determine validity and diagnostic accuracy of the 4AT as a means of assessing for delirium recovery versus the reference standard of a DSM-5 delirium diagnosis, in medical and surgical older hospitalised patients.

2.1.2 Secondary Objectives

The secondary objective is to determine if additional neuropsychological tests improve the performance of the 4AT in assessing delirium recovery.

2.2 ENDPOINTS

2.2.1 Primary Endpoints

(1) Diagnostic accuracy: sensitivity, specificity, positive and negative predictive values of the 4AT (and any supplementary cognitive tests) versus a reference standard delirium assessment at each set of paired assessments (except for the first assessment where all patients have delirium) in an older general acute medical and surgical hospital population.

- Sensitivity: the probability of the 4AT identifying those with delirium.
- Specificity: the probability of the 4AT in identifying those who don't have delirium.
- Positive Predictive value: the probability that a person with a positive 4AT test for delirium truly has the delirium.
- Negative Predictive value: the probability that a person with a negative 4AT test does not have delirium.

(2) Responsiveness of the 4AT (and any supplementary cognitive tests) to change in delirium status over time, via the concordance between within-person changes observed on the reference standard and on the 4AT.

2.2.2 Secondary Endpoints

Association of critical variables such as age and previous health status with the probability of transitioning across different delirium states (from full syndromal delirium to full recovery).

3. STUDY DESIGN

The research consists of two study phases:

Phase 1: Feasibility and pilot study
Phase 2: Validation study

These are observational studies involving brief bedside tests of cognitive functioning administered to the patient. There are no treatments or invasive investigations.

Phase 1: 30 participants aged 70 years and over with a diagnosis of delirium will be recruited from acute general medical and surgical wards of the Royal Infirmary of Edinburgh, over a period of 3 to 5 months. Each participant will be assessed on 2-4 occasions (up to 4 weeks).

Phase 2: 150 participants aged 70 years and over with a diagnosis of delirium will be recruited from three populations: cardiac surgery, hip fracture, and acute medical inpatients in the Royal Infirmary of Edinburgh, over a period of 15 months. Each participant will be assessed for up to 4 weeks.

In both study phases, participants will be visited by two different researchers on the same day. The first visit will involve assessment of capacity and (in those thought likely to be capable of giving consent) obtaining informed consent, as well as assessment of delirium and cognition lasting up to 20 minutes. The second visit will involve the 4AT assessment plus supplementary brief cognitive tests lasting up to 10 minutes. Where the participant is unable to provide consent for themselves, proxy consent will be sought, and if granted, the same visits as above will occur. The reference standard and 4AT assessments (plus supplementary tests) will take place within a maximum of three hours of each other, with a target interval of 15-60 minutes.

The reference standard and 4AT assessments will be repeated on one or more further days in the course of up to 4 weeks following recruitment into the study.

What will happen to the research participant?

(1) The participant will be approached by a member of the direct clinical team to assess willingness to hear more about the study. If this is the case, the member of clinical staff introduces the researcher to the participant.
(2) The researcher explains the study to the participant.
(3) Capacity assessment followed by consenting if appropriate will be performed by a trained researcher.
(4) Two different researchers will administer brief bedside tests of cognition (i.e. attention, memory and thinking). The first assessment will always be the reference standard assessment lasting up to 20 minutes. The second assessment (after a short break) will be the 4AT plus supplementary cognitive tests lasting up to 10 minutes. The reference standard assessments and 4AT (plus any supplementary tests) will be repeated over four weeks.

In line with COVID-19 government regulations, research staff will comply with physical distance measures as much as possible, and Personal Protective Equipment (PPE)

will be worn by researchers at all times whilst on the ward; this includes during interactions with research participants and the clinical team. Research staff will be trained in the appropriate use of PPE, and will receive COVID-19 vaccinations prior to the start of the study. Researchers will comply with local testing policies.

Study materials (laminated sheet, pens, etc.) will be disinfected before and after each use.

Assessment results blinding

The researchers will be blinded to the other's results. The results of the assessments will be recorded in the patient's records, and communicated to the patient's clinical team. The responsibility for the likely clinical diagnosis of delirium and subsequent management will remain that of the patient's clinical team.

Timing of assessments

Given the fluctuating nature of delirium, the reference standard assessment and the 4AT (plus supplementary tests) need to be completed within a short period of time. They will be completed within a maximum of 3 hours of each other, with a target interval of 15-60 minutes.

The duration of consent and bedside testing may last up to 40 minutes, whereby the consenting (10 minutes), reference standard assessment (up to 20 minutes) and 4AT plus supplementary tests (up to 10 minutes) are conducted serially.

Some participants may complete the study assessments a few hours following the consent process, or on a later date (typically the day following giving consent).

The bedside testing will be repeated on further occasions over four weeks. Thus, the total time that participants are in the study may be up to four weeks.

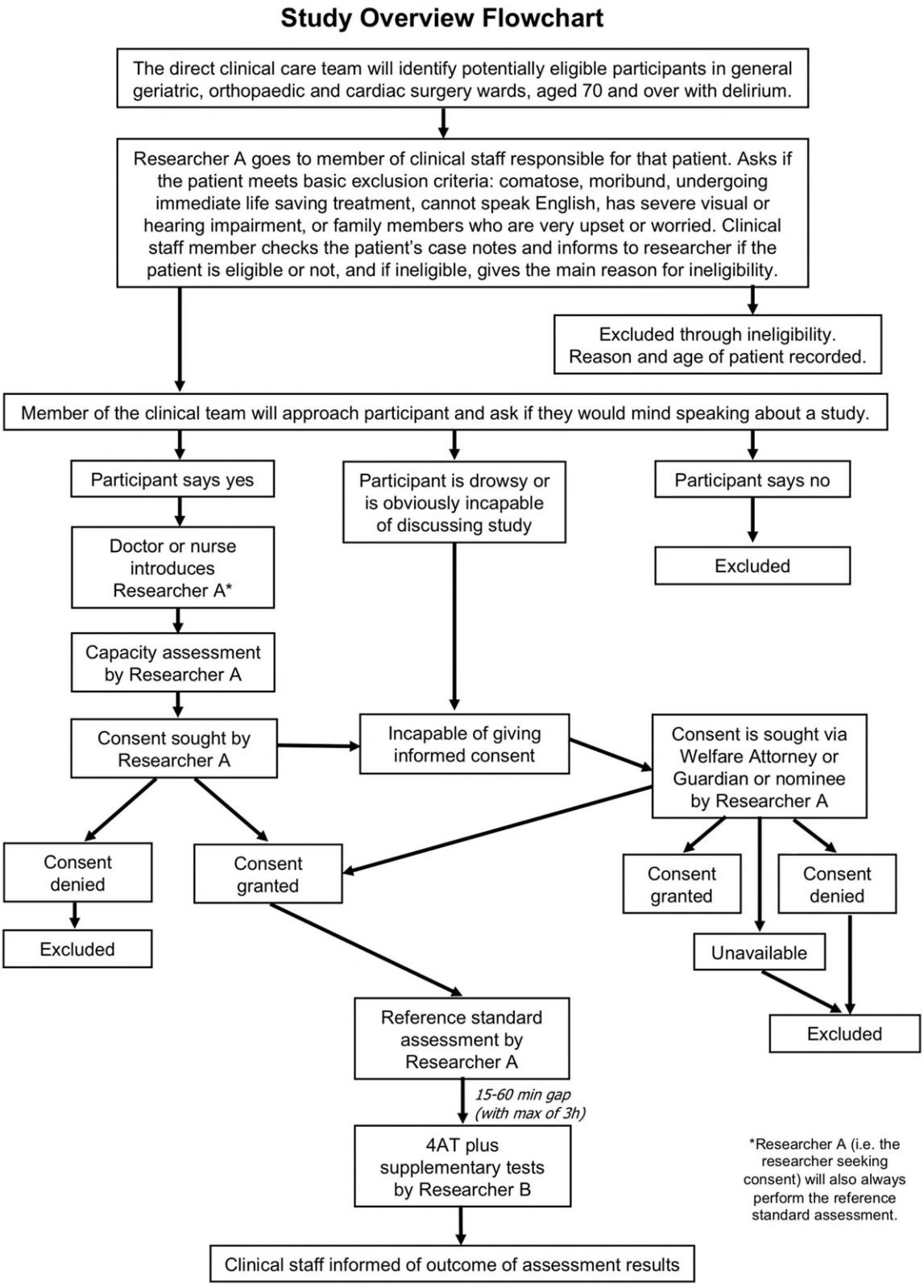

Figure 1: study overview flow chart.

4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit 180 participants, 30 for the Phase 1 study and 150 for the Phase 2 study from three populations: cardiac surgery, hip fracture and acute medical admissions in the Royal Infirmary of Edinburgh (10-15 participants per month). This is feasible as between the three sites there are several thousand potentially eligible patients admitted per year, with delirium rates of 15-25% in each group.

4.2 INCLUSION CRITERIA

- Surgical (cardiac and hip fracture) and medical patients with current delirium;
- Aged 70 years or over;
- Capacity to provide written, informed consent or the availability of a suitable relative or welfare guardian/attorney who is able to provide informed consent on behalf of the patient.

4.3 EXCLUSION CRITERIA

- Unable to communicate in English (some of the cognitive tests used have not been validated in non-English speakers, hence the study only includes patients who can normally communicate fluently in English), including severe dysphasia;
- Acute life-threatening illness requiring time-critical intervention;
- Coma;
- Vision or hearing impairment severe enough to preclude testing or interview;
- Photosensitive epilepsy;
- High level of patient and family distress, as judged by the clinical team.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

The process of identifying participants and obtaining consent described below follows the process agreed in prior Scotland A Research Ethics Committee applications (e.g. 15/SS/0071, 15/SS/0104, and 16/SS/0028).

Eligibility screening will take place between approximately 0800 and 2000. To identify potentially eligible patients, the researcher will ask ward staff for a list of names of patients who are in their care and who fulfil the basic inclusion criteria (see paragraph 4.2 and 4.3).

Then further eligibility screening will be carried out by a doctor or nurse responsible for the care of the patient. Specifically, the researcher will systematically gather detailed information about the patient from the doctor or nurse, using a formal checklist to identify any exclusion criteria. Case notes will be screened by the member of the clinical care team during this process. If patients are ineligible for the study, the reason for ineligibility and the age and sex of the patient will be recorded.

If the patient fulfils the eligibility screening criteria, a member of the patient's direct clinical care team will approach the patient to ask if a researcher can come to talk to them about taking part in the study.

If the patient expresses an interest in taking part in the study, the doctor or nurse will introduce the researcher to the patient.

The researcher (a trained psychology research associate or research fellow, or a trained nurse from the clinical team assisting with the study) will seek consent from the patient (or legal proxy, in the event the patient lacks capacity).

Patients may be asleep when first approached. This is very common in older inpatients with delirium, and gentle verbal prompting is acceptable. However, patients with delirium may be abnormally drowsy and difficult to rouse. The researcher will use their judgement as to whether the patient can be roused sufficiently to have a brief conversation about the study.

Patients who are intermittently drowsy or inattentive may lack capacity to decide on consent. In each case the capacity will be assessed and if not present at the time of assessment, the researcher will seek agreement from a legal proxy (refer to section 5.2 'Lack of capacity to consent').

The healthcare team may use their clinical judgment to decline approaching a potentially 'eligible' patient, perhaps due to patient or family distress. If the reason for not approaching the patient later resolves, the clinical team may decide that the patient can be approached on another occasion.

5.2 CONSENTING PARTICIPANTS

Informed consent will be sought by the researchers using a combined informal capacity assessment / consent process. Both verbal and written information will be provided about the study.

To determine if the participant has capacity, the researcher will briefly explain the following points, checking frequently that the patient can understand what is being said:

- They are being asked to help with a research project.
- The project is looking at a new method for measuring thinking and concentration in hospital patients.
- They will be asked to complete a few short tests that will measure their ability to think and concentrate.
- If they agree to take part, they will be tested on two occasions by two different researchers on the same day, usually within the same hour. The whole test procedure (assessment visit 1 and 2 combined) will take up to 30 minutes.
- They will be tested on up to 4 days (over the period of up to four weeks) during their stay in hospital.
- They can take as much time as they need to decide if they want to take part in the study, and they can speak with a friend or relative about this first if they wish.
- They do not have to take part. If they do decide to take part, then they can choose to stop taking part at any time, without having to give a reason. A decision to take part or to stop taking part will not affect their medical care in any way.

- The researcher will have to look at the participant's case notes and will also discuss their case with staff and relatives to find out how they have been doing.
- Information gained from the study will be passed to the participant's clinical team.

The researcher will ask the potential participant to recount the study information to check understanding and assess capacity to consent. Patients who express an interest in taking part, and who show capacity for informed consent, will be given an information sheet to read (or the sheet will be read to them by the researcher), and then invited to sign a consent form.

Consent will be sought for:
- Conducting assessments as specified in the study information sheets.
- Assessing health records for information relevant to the study.
- Recording this data in secure databases.
- Sharing of data with clinical team.

If a patient is unable to sign or mark a document to indicate their consent, arrangements will be made for their consent to be witnessed by another member of the clinical team, who is independent from the research study team. The researcher and the additional member of the clinical team will both sign the consent form.

Patients will be given as much time as they require to decide, within the constraints of the study. In some cases, patients will not be able to take part if they are discharged or die before the assessment takes place.

Once participants are enrolled in the study they will be given an information sheet with contact details for the research team and instructions on what to do if they wish to withdraw consent or require further information. There will be a nominated person whom patients/relatives/carers can approach at any time during their participation in the study if they have a question or concern.

Some participants will proceed with the two assessments immediately after completion of the capacity/consent process.

Due to the fluctuating nature of delirium, it is possible that the participant's capacity to give consent will fluctuate. This is a small risk for participants who can proceed with the assessments immediately after the consent process, given the whole process should be completed within about 3 hours.

However, if there is a longer interval between the consent/capacity process and assessments, there is a larger risk of a change in the participant's capacity (refer to 'Lack of capacity to consent' section).

Longitudinal assessments

Participants will be asked to provide consent to subsequent assessments even if at the time of these subsequent assessments they lack capacity. However, during the subsequent assessments, it will be carefully checked if the participant assents to continue their participation in the study. In participants who initially lack capacity and have been included through consent from a legal proxy, and who are undergoing serial assessments, researchers will assess the participant's capacity to consent at the

beginning of each new testing session. If the participant regains capacity after the final assessment, we will seek retrospective consent from the participant where possible.

Lack of capacity to consent

It is essential that the study recruit patients who reflect the relevant clinical population (i.e. hospitalised older patients with delirium).

Many patients with delirium lack the capacity to give consent for themselves. This applies particularly to patients with more severe delirium. It is critical to the value of the study that patients with delirium at different levels of severity are recruited, so that the findings are applicable to clinical practice.

If a patient does not understand, or if there is any doubt about the patient's capacity to give consent, the researcher will approach an appropriate legal proxy to ask if they would be willing to consider hearing about a study involving the patient, and to potentially give consent on their behalf. The only people that can consent on behalf of another in Scotland are Personal Legal Representatives, that is Welfare Attorney, Welfare Guardian or nearest relative (this is the order that they must be approached to seek consent).[19] This initial approach will be via telephone if the legal proxy is not physically present at the time of recruitment, because unnecessary delays in achieving consent will compromise the validity of the study. Importantly, the researchers will only proceed with telephone consent if the clinical care team feels that this was appropriate. In such cases where consent is sought via telephone, a verbal description of the study (covering all the same information as for a patient with capacity) will be provided, with an opportunity to ask questions. The person will be asked for advice on whether the patient should take part in the study and what, in their opinion, the patient's views and feelings would have been on taking part in the study, had they retained capacity. This process will be witnessed by a member of the clinical team who is not connected with the study. The witness will use a Telephone Witness Checklist during the telephone consent process to ensure that all relevant information is conveyed to the patient's nearest relative, guardian or welfare attorney.

Recruitment of patients who lack capacity proceeds under the provision of the Adults with Incapacity (Scotland) Act 2000.[19] If no appropriate legal proxy can be identified, the patient will not be recruited to the study.

If there is a longer period between the capacity/consent process and the beginning of the assessments, due to the fluctuating nature of delirium, it is possible that a participant's capacity may be lost or regained in the intervening period. The researcher will need to ensure that the capacity and consent remains valid just prior to the assessments being completed.

- If a participant later regains their capacity after proxy agreement has been obtained, they will be given an opportunity to provide informed consent for themselves.
- If the researcher becomes aware the participant, who originally had capacity, has lost capacity, the assessments will continue in view of their previous consent.

If a patient indicates a clear reluctance to take part, whether or not they have capacity, they will be excluded at this stage.

5.3 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form. We will aim to keep and use data already collected in each case unless the patient or proxy opt to have all data collected removed. To safeguard the patient's rights, the minimum personally-identifiable information possible will be collected.

Stopping rules/discontinuation criteria

There are no formal early stopping rules, however the trial will be stopped if it is not possible to recruit patients.

6. STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

On a single test day, each participant will undergo a reference standard assessment for delirium (lasting up to 20 minutes) by the researcher who conducted the capacity assessment and sought consent (Researcher A in Figure 1). A different researcher will also ask each patient to undergo the 4AT plus supplementary brief cognitive tests (lasting up to 10 minutes; Researcher B in Figure 1).

The reason that researchers doing the capacity assessment and consenting process must also do the reference assessment, is that the capacity and consenting process provides information over and above the normal 4AT testing. This is not an issue for the reference standard assessment, which is aimed at providing a thorough assessment as to provide excellent diagnostic accuracy.

The order of the assessments is fixed (first reference standard assessment, then 4AT assessment). The assessments will be completed on Case Report Forms. The data will be transcribed to a secure database, using only link anonymised codes. The results of the 4AT scores will be added to the patients' medical records and the scores verbally communicated to the clinical team.

Reference standard assessment

The reference standard is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for delirium[1]. This will be centred on the Delirium Rating Scale-Revised-98 (DRS-R98)[20], a well-validated scale which assesses multiple dimensions of mental status change and quantifies delirium severity. As per the instruction manual, the DRS-R98 will be supplemented with short neuropsychological tests of attention and other domains. As patients with delirium are typically poor at focusing and/or maintaining attention, the tests will be brief and instructions will be kept simple.

We will also record any formal prior diagnosis of dementia and Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE)[21] scores. The IQCODE is a widely used validated questionnaire which assesses whether an individual has pre-existing cognitive impairment. It is administered to the nearest relative or carer and takes 5 minutes to complete. An information sheet on the IQCODE will be given to the legal proxy (the proxy will often be the person asked to complete the IQCODE). The use of the IQCODE in the present study follows the process that was used in recently completed Scotland A REC-approved studies (e.g. ref no. 15/SS/0071 and 15/SS/0104).

The reference standard assessment will involve inspection of case notes, patient observation and discussion with the clinical team and informant, if available. It will take up to 20 minutes of the patient's time in total.

The DRS-R98 and supporting tests will be used to inform a diagnosis of delirium based on DSM-5 criteria.

The 4AT

The 4AT[17] comprises 4 items (Appendix 1).[7] Item 1 concerns an observational assessment of level of alertness. The next 2 items are brief cognitive tests: the Abbreviated Mental Test – 4 (AMT4) which asks the patient to state their age, their date of birth, the current year, and the place they are in; and attention testing with Months Backwards, in which the patient is asked to state the months of year in reverse order, starting with December. Only items 1-3 are done at the bedside, and the typical duration is under 2 minutes. Item 4 concerns acute change in mental status, a core diagnostic feature of delirium; this information is obtained from the case notes or the GP letter or from an informant.

The 4AT has a total possible score of 12. Scores of 0-3 will give a ‘no delirium’ classification, and scores 4-12 give a ‘delirium’ classification.

7. DATA COLLECTION

7.1 Source Data Documentation

A written paper log will be kept with the unique identifier code adjacent during the process of seeking consent. The participant or informant consent forms will also be kept, and these will have the participant’s name on it. Data containing patient identifiable information will be stored in locked filing cabinets in locked offices in the Geriatric Medicine Unit of the University of Edinburgh, located in the Royal Infirmary of Edinburgh.

The actual study documents with cognitive test data (4AT and reference standard assessment) will only have the identifier code on them. The link between the participant’s name and identifier code will be stored separately to the records of cognitive test data.

The data will be recorded on electronic or paper Case Report Forms (to be determined), and later transcribed onto a secure database, using only link anonymised codes. Quality checking will be performed in 10% of Case Report Forms. Personal identifiable information will not be stored electronically.

Outcome measures, including length of stay, adverse events in hospital (such as falls), discharge location and mortality, will be collected around 12 weeks post-recruitment. Further outcome data including mortality will be obtained over a 10-year period from electronic records. This information is required when describing the study cohort in scientific papers.

7.2 CASE REPORT FORMS

Data will be recorded on paper Case Report Forms:

- Participant Medical Information Case Report Form: this will include standard demographic variables, clinical history and current medication (Researcher A).
- Reference Standard Assessment Case Report Form (Researcher A).
- 4AT assessment Case Report Form (Researcher B).

8. DATA MANAGEMENT

8.1 PERSONAL DATA

The following personal data will be collected as part of the research: name, date of birth, sex, clinical and medication history.

Personal data will be stored by researchers in a locked filing cabinet in the Geriatric Medicine Unit, Royal Infirmary of Edinburgh. The researchers and study PI will have access to personal data. The key to linking the personal data to the assessment data will be stored in a locked cabinet in a locked office in the Geriatric Medicine Unit, separately from all other data. Personal data will be stored for 10 years, to allow full analysis of the data. Also, information from this study will be used to inform future research in the coming years. It will be necessary to have access to this information in case of the need to perform additional analyses or comparisons if further information comes to light.

8.2 TRANSFER OF DATA

Personal data collected or generated by the study will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s). Fully anonymised datasets may be shared with appropriate organisations.

8.3 DATA CONTROLLER

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The University of Edinburgh and NHS Lothian are joint data controllers for this study.

8.4 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9. STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

We will recruit 150 patients with delirium, of whom approximately 90 will have made a recovery by DSM-5 criteria in the study assessment window (figures estimated from existing literature[13] and local data[22] in a hip fracture population in which of patients with delirium on post-op day 1, 42% had delirium at day 4).

Based on this sample size and a true sensitivity and specificity of 0.7-0.9, the 2-sided 95% confidence interval width for specificity would range from ±0.062 to ±0.095, and for sensitivity from ±0.076 to ±0.116.

Our previous studies involving longitudinal assessments in over 400 hospital inpatients (N=30-108 per study, ~15% delirium) found large effect sizes (Cohen's d 2.5-3) for within-person differences on cognitive tests in patients transitioning from delirium to no delirium, indicating sufficient power to detect clinically meaningful changes.

9.2 PROPOSED ANALYSES

The analyses will be carried by the study team which includes the study statistician Dr Graciela Muniz-Terrera if the University of Edinburgh. The statistical analysis plan will be agreed prior to database lock.

Primary analyses:
(1) Assessment of diagnostic accuracy of the 4AT (and supplementary cognitive tests): cross-sectional comparison of 4AT versus the reference standard will be determined at each set of paired assessments using sensitivity, specificity, and positive and negative predictive values, and area under the ROC curve (except for the first assessment where all patients have delirium); this will allow determination of whether the accuracy of the 4AT under conditions of repeated assessments is similar to its known cross-sectional performance.

(2) Evaluation of responsiveness to change in delirium status over time: longitudinal evaluation of responsiveness to change in delirium status (including recovery from delirium) will be assessed using generalised linear mixed effects models, to determine if a within-person change in delirium diagnosis by the reference standard is reflected in 4AT scores.

Secondary analyses:

(3) Multi-state models will be fitted to evaluate the association of critical variables such as age and previous health status with the probability of transitioning across different delirium states (from full syndromal delirium to full recovery).

Descriptive statistics on the concordance between changes observed on the reference standard and on the 4AT will also be presented.

10. OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11. GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks will be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasized that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by representatives of the sponsor(s). The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

11.3 STUDY SITE STAFF

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.4 DATA RECORDING

The Principal Investigator is responsible for the quality of the data recorded in the Case Report Form at each Investigator Site.

11.5 INVESTIGATOR DOCUMENTATION

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

11.6 GCP TRAINING

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

11.7 CONFIDENTIALITY

All evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.8 DATA PROTECTION

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

12. STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorization before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot.

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.5 END OF STUDY

The end of study is defined as the last participant's completion of all assessments.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.6 INSURANCE AND INDEMNITY

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

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Appendix 1: The 4AT.

4AT

Assessment test for delirium & cognitive impairment

(label)

Patient name:

Date of birth:

Patient number:

Date: **Time:**

Tester:

CIRCLE

[1] ALERTNESS

This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	**0**
Mild sleepiness for <10 seconds after waking, then normal	**0**
Clearly abnormal	**4**

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	**0**
1 mistake	**1**
2 or more mistakes/untestable	**2**

[3] ATTENTION

Ask the patient: "Please tell me the months of the year in backwards order, starting at December."
To assist initial understanding one prompt of "what is the month before December?" is permitted.

Months of the year backwards	Achieves 7 months or more correctly	**0**
	Starts but scores <7 months / refuses to start	**1**
	Untestable (cannot start because unwell, drowsy, inattentive)	**2**

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (eg. paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs

No	**0**
Yes	**4**

4 or above: possible delirium +/- cognitive impairment
1-3: possible cognitive impairment
0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE ☐

☐

GUIDANCE NOTES Version 1.2. Information and download: **www.the4AT.com**

The 4AT is a screening instrument designed for rapid initial assessment of delirium and cognitive impairment. A score of 4 or more *suggests* delirium but is not diagnostic: more detailed assessment of mental status may be required to reach a diagnosis. A score of 1-3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. A score of 0 does not definitively exclude delirium or cognitive impairment: more detailed testing may be required depending on the clinical context. Items 1-3 are rated *solely on observation of the patient at the time of assessment.* Item 4 requires information from one or more source(s), eg. your own knowledge of the patient, other staff who know the patient (eg. ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.

Alertness: Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item. **AMT4 (Abbreviated Mental Test - 4):** This score can be extracted from items in the AMT10 if the latter is done immediately before. **Acute Change or Fluctuating Course:** Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, "Are you concerned about anything going on here?"; "Do you feel frightened by anything or anyone?"; "Have you been seeing or hearing anything unusual?"

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