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Development and validation of the 4AT: a new rapid screening tool for delirium

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List of Abbreviations

4AT: 4 “A”s Test
AMT4: Abbreviated Mental Test - 4
CAM: short Confusion Assessment Method
CI: Confidence Interval
CRF: Case Record Form
DRS-R98: Delirium Rating Scale – Revised - 98
DSM-IV: Diagnostic and Statistical Manual for Mental Disorders, 4th Edition
ED: Emergency Department
ICD: International Classification of Diseases
IQCODE: Informant Questionnaire for Cognitive Decline in the Elderly
SAP: Statistical Analysis Plan

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 DSM-IV criteria for delirium are, in summary: a disturbance of consciousness (that is, reduced ability to focus, sustain or shift attention), and a change in cognition. The mental status deterioration develops over short periods of time (usually hours to days) and it tends to fluctuate[1]. Delirium is commonly precipitated by acute illness, trauma, or the side-effects of drugs. The presence of a 'general medical condition' is also part of the Diagnostic and Statistical Manual for Mental Disorders, 4th Edition (DSM-IV) criteria. Delirium is extremely common: it affects at least 15% of patients in acute hospitals[2-4]. It is independently associated with many poor outcomes [5-9]. Delirium is also a marker of current dementia [5,10] and is associated with acceleration of existing dementia[11]. In older patients without dementia, an episode of delirium strongly predicts future dementia risk[6,12]. The economic burden of delirium derived from 2008 US data estimates the one-year health care costs to be $38-$152 billion[12].

Detection of delirium is essential because it indicates acute systemic or central nervous system illness, physiological disturbance and drug intoxication or withdrawal. Failure to detect delirium in the acute setting is associated with worse outcomes[13]. Specific management of delirium is of obvious and immediate benefit to patients in many clinical situations, e.g. in reversing opioid toxicity, treatment of peripheral infections which have presented with delirium, alleviating distress caused by delusions and hallucinations[14], and in prompting more thorough assessment of symptoms. For example, some studies have found that surgical patients with delirium receive less analgesia than those with normal cognition[15]; this matters not only because pain treatment is an end in itself but because pain is itself a cause of delirium.

More broadly, detecting cognitive impairment in general (delirium, dementia, depression, learning disability, etc.) is a prerequisite for high quality care because of the multiple immediate implications of cognitive impairment for patients and staff, including: ensuring adequate communication with the patient and their families, doing careful assessment of capacity to provide consent for clinical procedures, avoiding giving treatments contrary to the law because of lack of consent, alleviating distress more readily, avoiding unnecessary bed transfers, and prompting delirium prevention including a detailed drugs review. Detection of dementia has recently been highlighted in the Dementia Commissioning for Quality and Innovation framework in operation in NHS England[16]; crucially, establishing if the patient has a 'clinical diagnosis of delirium' is a central element in the FAIR (Find, Assess, Investigate, Refer) algorithm at the heart of this framework.

Under-detection of delirium: There is ample evidence that in general medical and Emergency Department settings that delirium is grossly under-detected: at least two-thirds of cases are missed[4,17,18]. It is unclear why detection rates are so low. Evidence from surveys and workshops have raised several possibilities, including general ignorance about delirium, lack of awareness of its importance, uncertainty about discriminating delirium from dementia, and lack of time for assessment in the acute setting[19-23]. For example, in a survey of 784 UK trainee physicians, only 21% stated that they had good knowledge of the diagnostic criteria for delirium; and only 8% reported using specific screening tools for delirium[19]. Taken together, these findings strongly suggest that the lack of a very rapid, simple, and validated screening tool is a major factor in the under-detection of delirium.

Though many delirium assessment instruments have been developed that operationalise the standard diagnostic criteria for delirium, these have largely remained research tools. The most commonly advocated screening tool for use in routine clinical care, the short Confusion Assessment Method (CAM), has satisfactory sensitivity and specificity in trained hands but takes 5-10 minutes to complete because it requires a cognitive assessment like the Modified Mini-Cog[24,25] to be done first. The CAM also requires the rater to make subjective judgement of mental status. Subjective judgements are less reliable, often more time-consuming, and more difficult for staff (particularly non-specialists) than simple objective measures with clearly-defined cut-points. For example, a recent study using trained assessors found a kappa of 0.66 for the subjectively-rated CAM inattention item[25].

The problem of 'untestability' is likely to be another important factor in delirium under-detection: many patients in acute settings are too unwell, sleepy, or agitated to undergo cognitive testing or even interview[26-29]. Most screening tools, including the CAM, do not make explicit how these patients should be classified. The result is that mental status assessments are simply left uncompleted in most 'untestable' patients, and no diagnosis, and often no specific treatment, is applied. This lack of a diagnosis is harmful to patients[13].

Finally, given the time pressures in acute settings, it is challenging to implement a separate delirium screening instrument in addition to any existing general cognitive screening instruments. The lack of a combined instrument allowing screening for both general cognitive impairment and delirium may therefore contribute to the lack of specific delirium detection. Early diagnosis of delirium using evidence-based diagnostic tools offers a means for improved outcomes and more efficient resource-allocation decisions. To inform priority setting objectives, a health economic component will be integrated into the study to evaluate the delivery costs of the 4AT and CAM from the perspective of the UK National Health Service.

1.2 Rationale for the Study

Given the multiple constraints of the acute environment, the range of staff that might be expected to screen for delirium, the common co-existence of delirium and dementia, and the heterogeneity of patients, we judged that a screening tool should have these features:

1. *Short (less than 2 minutes)*
2. *Easy to learn*
3. *Easy to administer and score*
4. *Can be used by professional-level healthcare staff from a variety of disciplines*
5. *Allows scoring of patients who are too drowsy or agitated to undergo cognitive testing or clinical interview*
6. *Takes account of informant history*
7. *Can be administered through written questions to people with severe hearing impairment*
8. *Can be administered to patients with visual impairments*
9. *Does not require subjective judgements based on interview*
10. *Combines delirium screening with general cognitive screening*
11. *Does not need a quiet environment for administration*
12. *Does not require physical responses such as drawing figures or clocks*

There are multiple instruments for delirium screening, diagnosis, severity assessment, and monitoring[30-33]. Before deciding to design a new screening tool, we therefore examined each of the available tools against the above criteria, focusing on screening tools such as the CAM. We also searched the literature systematically, including conference proceedings, books, and book chapters, for any newly-published tools as well as to examine the study data for each tool. Most scales were excluded on grounds of duration alone. The remaining scales lacked features such as general cognitive screening, and other important features. We thus found that, in late 2010, no existing tool fulfilled the above requirements, and because of this we decided to design a new test. This conclusion was supported by the NICE Guidelines on Delirium[5] which emphasised the need for research on a screening tool for delirium suitable for routine use.

The subsequent design process involved scrutiny of each of the nearly 30 published delirium assessment tools, evaluating the performance of each, including subtests, in published studies and, in most cases, through direct clinical or research experience of their use. Because we had decided to incorporate general cognitive screening into the new instrument, to avoid the need to have separate instruments for cognitive screening and delirium screening, we also reviewed the broader literature on brief tests for general cognitive impairment (including dementia). In the context of designing a screening tool for the acute hospital, it is important to note that delirium generally causes cognitive impairment detectable on the kinds of tests used for dementia screening[34,35]. Therefore, abnormal test results may indicate delirium and/or dementia (as well as other causes of cognitive impairment, such as learning disability). It is clinically essential to know if any such impairment is acute, that is, delirium, but also important to identify underlying general (acute or chronic) cognitive impairment. A tool designed exclusively to detect cognitive impairment will not lead to delirium detection without another step, and a tool designed only to detect delirium may miss general cognitive impairment. In this light, we decided that the 4AT should include cognitive screening sensitive to general cognitive impairment, but also including items on altered level of alertness and change in mental status, both of which are strong indicators of delirium.

The first version of the 4AT was drafted and tested informally by colleagues, changes were made based on feedback, and updated versions tested again. After several iterations involving 20 doctors and nurses of varying levels of experience, the final version was produced. An initial audit in 30 inpatients comparing clinical use of 4AT with independent reference standard DSM-IV assessment found 100% sensitivity (CI 69-100) and 90% specificity (CI 68-99). A recent validation study in Italy involving 234 consecutively recruited older hospitalised patients found that the 4AT had a sensitivity of 89.7% and specificity 84.1% for delirium. The area under the receiver operating characteristic curves for delirium diagnosis was 0.93[36]. Since the 4AT was launched, locally and through the www.the4AT.com website, it has been adopted in clinical units in several centres in the UK and internationally. Feedback from these sites has been mainly positive. We have also recently conducted an anonymised survey of 4AT users (N=101), which also showed mainly positive views of the accuracy and usability of the 4AT in clinical practice.

Thus, there is encouraging evidence that the 4AT has value as a tool for delirium detection in routine practice. This evidence comes from several sources: one published study, audits in several sites, informal feedback, adoption in clinical practice by several clinical units globally, and a recent web-based survey focused specifically on 4AT use evidence supporting its use. However, a formal validation study is now necessary to provide definitive evidence of the diagnostic accuracy of the 4AT. Comparison with the CAM is also of value, because the CAM is in use in some clinical units and thus information on how the 4AT performs in relation to the CAM will help clinicians decide which tool is

suitable for their particular context. Further information on how the 4AT performs as a cognitive screening tool, its ability to predict outcomes, and how each item of the 4AT contributes to its diagnostic accuracy will also provide important guidance to clinicians. Finally, understanding the economic costs of performing the 4AT and the CAM will help service managers to determine cost-effectiveness.

2. STUDY OBJECTIVES

2.1 Primary and Secondary Objectives

The primary objective of the study is to determine the diagnostic accuracy of the 4AT for delirium detection versus the reference standard of a DSM-IV diagnosis.

The secondary objectives are: (a) to compare performance of the 4AT and the Confusion Assessment Method (CAM), (b) to determine if the 4AT is an adequately sensitive tool for detecting general cognitive impairment as judged against a documented history of dementia and/or the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE); (c) to determine if 4AT scores predict important outcomes such as length of stay, institutionalisation, and mortality, up to 12 weeks; (d) to determine the performance of individual items of the 4AT, e.g. how accurate is altered level of alertness alone as a predictor of delirium diagnosis?; (e) to assess the 4AT total score as a measure of delirium severity; (f) to estimate the delivery costs of the 4AT and CAM as a function of their diagnostic performance up to 12 weeks as well as modelling longer term resource consequences.

2.2 Primary and Secondary Endpoints

(1) Primary endpoint:

Diagnostic accuracy (positive and negative predictive values, sensitivity and specificity) of the 4AT versus the reference standard delirium diagnosis

(2) Secondary endpoints:

(a) 4AT versus CAM in relation to reference standard delirium diagnosis

(b) Performance of 4AT cognitive test items (AMT4 and Months Backwards) in detecting longer-term cognitive impairment as detected by the IQCODE

(c) 4AT total scores as a predictor of the following clinical outcomes as determined at 12 weeks post-test: length of stay, institutionalisation (as assessed by proportion of patients newly admitted to care homes or awaiting care homes at that time) and mortality

(d) Performance of individual items of the 4AT in relation to reference standard delirium diagnosis

(e) We will assess the 4AT total score as a measure of delirium severity by calculating the Spearman correlations between 4AT and DRS-R98 scores and its 95% confidence interval.

(f) The primary output from the health economic analysis will be a comparison of the service delivery costs associated with the diagnostic accuracy of alternative (4AT vs. CAM vs. reference standard) triage tools for delirium.

3. STUDY DESIGN

3.1 Summary of study design

900 patients aged 70 or over in Emergency Departments or acute general medical wards will be recruited in three sites (approximately 300 patients per site over a period of 18 months. Each patient will undergo (a) a reference standard delirium assessment lasting up to 20 minutes, and (b) either the 4AT or the CAM (lasting up to 10 minutes). The reference standard and 4AT or CAM assessments will take place within a maximum of two hours of each other, with a target interval of 15 minutes. The team will also administer a questionnaire on pre-admission cognitive function to an appropriate informant (if one is available). This will be completed within 4 weeks of the patient being recruited to the study assuming an appropriate individual is available.

At 12 weeks the team will also administer a 10 minute resource use questionnaire (face to face in hospitalised patients, or by telephone when possible), and will access each recruited patient's medical records at 12 weeks to ascertain a set of key clinical outcomes including length of stay, institutionalisation, and mortality, as well as to derive further information on resource utilisation.

The study flowchart is shown in Figure 1.

3.2 Recruitment

Patients will be recruited between 08.00 and 22.00. Lists of all potentially eligible patients in batches will be generated and initial eligibility screening will be carried out by a member of the clinical team. Then, in alphabetical order, consent from patient (or legal proxy) or agreement from a consultee will be sought by a study researcher. Please see later sections for detailed information on the consenting process.

3.3 Consent

3.3.1 Assessing capacity and obtaining informed consent

Informed consent will be sought by a trained researcher. A combined informal capacity assessment/consent process will be used because a separate formal capacity test has been shown to exclude large numbers of potential participants in delirium studies[37]. Both verbal and written information will be provided about the study, using a style and format suitable for the participant group (i.e. for varying levels of capacity). The researcher will ask the potential participant to recount the study information to check understanding. This, together with the treating team views, will be used to assess capacity to consent. For participants judged to have capacity, consent will be sought for:

(a) Conducting assessments as specified in the study information sheets

(b) Accessing health records for the purpose of collecting information relevant to outcomes and patient health service use

(c) Recording these data in secure study databases

It will be made clear to potential participants, both verbally and in the participant information sheets, that they are under no obligation to take part, they do not have to give a reason for declining, and their

usual care will not be affected by their decision. Potential participants will also be told verbally and in writing that at any stage, they can withdraw consent without giving a reason, and without prejudice to their care. Once participants are enrolled in the study they will be given a 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 (the recruitment hub lead) at each study site, whom patients/carers can approach at any time during their participation in the study if they have a question or concern.

3.3.2 Lack of capacity to consent

It is essential that this study recruits patients which reflect the target clinical population. This means that we must recruit patients with delirium in the same proportion as in the clinical population. Not achieving this is a major risk in the present study, because many patients with delirium lack capacity to give consent. Patients who lack capacity to give consent are more difficult to recruit because of the need to involve a legal proxy, a consultee or other legal representative. Prior research has shown that difficulties in recruiting patients with delirium who lack capacity to consent can lead to biased and unrepresentative samples[37]. Therefore, to maximise the numbers of patients recruited and so as to make sure that patients recruited reflect the clinical population accurately we will seek consent/agreement from legal proxies, consultees or other legal representatives.

Where the potential participant is deemed to lack capacity to consent, recruitment will proceed under the provisions of the Mental Capacity Act, 2005 in England or Adults with Incapacity (Scotland) Act, 2000. The clinical team will be asked to identify an appropriate personal or nominated consultee, guardian, welfare attorney or nearest relative.

Because of differing legal requirements in Scotland and England, the details of the processes in each nation now follow.

Scotland

An appropriate legal proxy (that is, a guardian, welfare attorney, nearest relative, but not a member of the clinical team) will be approached by a member of the clinical team (potentially including researchers who are part of the clinical team) to be asked if they would be willing to consider hearing about a study involving the patient, and to potentially give consent on their behalf.

If the proxy assents to hearing more about the study, the study team member responsible for consent will provide the proxy with information about: why they are being approached; the role of a proxy, explanation that acting as a proxy is voluntary; details of the study (as would be given to a participant with capacity). The proxy will be asked for advice on whether the participant should take part in the study and what, in their opinion, the participant's views and feelings would have been on taking part in the project had they retained capacity. Consent forms will be signed when the proxy is physically present. If no appropriate legal proxy can be identified within 96 hours, the patient will not be recruited to the study. This is because in Scotland patients with incapacity cannot be included in studies of non-medicinal treatments unless there is a guardian, welfare attorney or nearest relative available to give consent.

England

If the patient is incapacitated at study entry then a personal consultee (usually a friend or relative) will be consulted and their opinion sought. The approach used will be similar to that detailed in the previous section when consulting legal proxies in Scotland.

If the personal consultee agrees that their friend/relative can enter the study then we would ask them to sign a declaration form.

If a personal consultee is not available for consultation then the treating doctor (who will be independent of the research team and of appropriate seniority), will be asked to act as the nominated consultee and advise on inclusion in the study. If agreement is given it will be recorded on the declaration form.

All Trial Participants (England and Scotland)

All patients who lack mental capacity at the time of enrolment will be approached for consent to remain in the trial at the earliest opportunity once they regain capacity. Research staff have planned contact with study patients on the day of enrolment and only on one further occasion at 12 weeks when they will collect questionnaire data from the patient. If research staff become aware the patient has regained capacity while in hospital then written consent from the patient will be sought at this time. It is likely that in many cases the first contact by the research team will be at 12 weeks either in person or by phone.

The patient will be given the opportunity to either withdraw or remain in the study at this time. If the patient chooses to withdraw from the study they will be given the option of allowing/not allowing the use of data already collected. A patient information sheet will be posted to participants who wish to remain on the study and other patients on request.

If patients have not regained capacity at 12 weeks they will remain in the study based on the advice of the consultee or legal proxy.

3.4 Patient assessments

3.4.1 Training in Assessments

Assessments will be carried out by researchers fully trained in background information on delirium, the features of delirium, and each rating scale. Training is carried out using written, video and bedside training until competence in all aspects of the assessments is achieved.

3.4.2 Reference Standard Assessment

Reference standard assessment: This will be centred on the Delirium Rating Scale-Revised-98 (DRS-R98)[38], a well-validated scale which assesses multiple dimensions of mental status change and quantifies delirium severity. The DRS-R98 includes 16 domains which are divided into two parts. The first part comprises 13 domains of mental status assessment which are rated according to their presence according to a three-point severity scale, or are absent. The second part comprises 3 items which are concerned with the diagnosis of delirium, namely ‘Temporal Onset of Symptoms’, ‘Fluctuation of Symptom Severity’ and ‘Physical Disorder’. The first two of these three require information from an

informant who is able to state if the patient is different from their baseline state. This means that the rater needs to inspect the casenotes, speak to staff who know the patient, or speak to the patient's relatives or others who know them. We will seek specific consent from the patient regarding approaching a relative or friend for this information. As per the instruction manual, the DRS-R98 will be supplemented by short neuropsychological tests of attention and other domains, including Digit Span[25], the Observational Scale for Level of Arousal[39], the Richmond Agitation Sedation Scale[40] and the DelApp objective attentional assessment[41].

To address the 4AT cognitive test item validation objectives we will also record any formal prior diagnosis of dementia and Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE)[42] scores. The IQCODE is a very widely-used validated questionnaire which allows estimation of whether an individual has pre-existing cognitive impairment. It is administered to the nearest relative or carer and takes 5 minutes to complete. Consent will be sought from the nearest relative or carer before the IQCODE data is collected. Although reasonable efforts will be made to collect this information, if there is not an appropriate person available within the 4 week time window then we will be unable to collect these data.

The DRS-R98 and supporting tests will be used to inform a binary ascertainment of delirium based on DSM-IV criteria. The final DSM-IV ascertainment of delirium will be based on a standardised process with final verification by the Chief Investigator, blind to the 4AT or CAM results. The panel of supporting tests, and the way the data are coded will be designed such that the performance of the 4AT can be evaluated against the DSM-5 criteria[43]. The reference standard assessment will take approximately 15-20 minutes of each patient's time.

3.4.3 The 4 "A"s Test (4AT)

The 4AT (see www.the4AT.com) comprises 4 items. 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 casenotes or the GP letter or from an informant, as per the DRS-R98.

3.4.4 Short Confusion Assessment Method (CAM)

The CAM is a diagnostic algorithm in which the tester rates the following four features as positive or negative: 1. Acute Change and Fluctuating Course; 2. Inattention; 3. Disorganised Thinking; and 4. Altered Level of Consciousness. The CAM scoring process requires that Features 1 and 2 are both positive; if they are positive then Features 3 and 4 are assessed and if one of Features 3 or 4 is positive, then the whole CAM is positive. The tester scores the features by a combination of interview with the patient, cognitive testing (the CAM requires that a cognitive test is performed before the features are scored), examining the casenotes, and seeking informant history if required. Note that the questionnaires used to assess cognition are not specified by the CAM manual, though some suggested tests are provided. Feature 1 is assessed by the same process as Item 4 in the 4AT. Feature 2 is assessed by the

tester giving a positive or negative rating to the question, "Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?" Feature 3 is assessed by the tester giving a positive or negative rating to the question, "Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?" Feature 4 is similar to item 1 in the 4AT. In this study, for the pre-CAM cognitive assessment we will use a set of questions covering the cognitive domains represented in the suggested tests in the CAM manual, including Days of the Week Backwards, counting from 20 down to 1, orientation questions, three-word recall, and clock-drawing. All of these questions are used in routine clinical practice at the bedside.

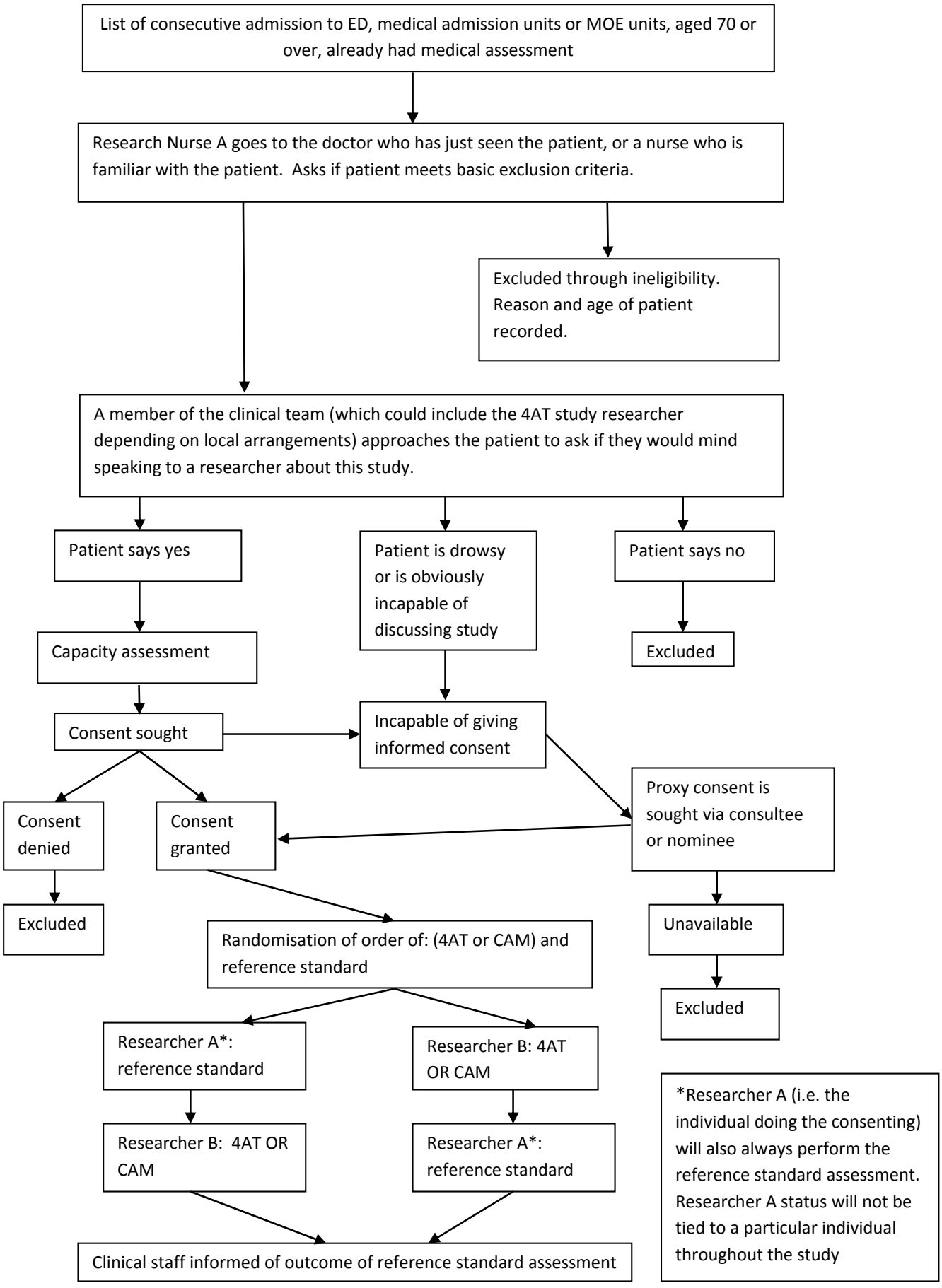
3.5 Ordering of assessments

All patients will undergo a reference standard assessment for delirium by the researcher who conducted the capacity assessment and consenting process. A different researcher will also ask each patient to undergo either the 4AT or the CAM. The reason that the researcher doing the capacity assessment and consenting process must also do the reference standard assessment is that the capacity and consenting process provides information to the tester over and above the normal 4AT or CAM testing process. This is not a concern for the reference standard assessment, which is aimed at providing a thorough assessment so as to optimise diagnostic accuracy.

The order of these two assessments ([4AT or CAM assessment] and reference standard assessment) will be randomised. This randomisation will happen immediately after consenting. This means that each patient will receive the reference standard assessment by the same researcher who did the capacity and consenting process. The 4AT or CAM will be performed by a different researcher. The randomisation will determine which order the patient receives each of the two tests.

When possible the IQCODE will then be administered to a person who knows the patient well (within 4 weeks of the patient joining the study).

Figure 1: study overview flowchart



4. STUDY POPULATION

4.1 Number of participants

The total number of participants is 900. There will be approximately 300 in each of the three study sites (Edinburgh, Bradford, and Sheffield).

4.2 Inclusion/exclusion criteria

Inclusion criteria:

- Aged 70 or over
- Acutely admitted to the Emergency Department (ED) (within 12 hours of attending) or acute general medical and geriatrics units (within 96 hours of admission to the ward). In the case of the ED patients, we will only recruit from those patients who were brought in by ambulance as an emergency or through their general practitioner, to ensure that we are recruiting patients who are more representative of those which are more likely to be admitted to hospital as well as have underlying cognitive impairment or other co-morbidities.

Exclusion criteria:

- Acute life-threatening illness requiring time-critical intervention e.g. ST-elevation myocardial infarction; septic shock; severe pulmonary oedema.
- Coma ('Unresponsive' on the AVPU scale[45])
- Unable to communicate in English, severe dysphasia.

4.3 Identification of participants

Patients will be recruited between 08.00 and 22.00. A list of potentially eligible patients will be generated in batches at the start of each recruitment period and initial eligibility screening will be carried out by clinical staff (including clinical research nurses embedded in the clinical team). Then, in alphabetical order, in each batch consent/agreement from patient (or proxy/consultee) will be sought by a study researcher. Numbers of those (a) initially potentially eligible (b) screened as non-eligible by clinical staff and (c) declining to take part will be recorded.

4.4 Co-enrolment

We will seek to recruit patients involved in other studies where the patient or proxy/consultee accedes to this and where appropriate co-enrolment agreements are in place.

4.5 Risks and Benefits to Participants

This is an observational study involving bedside interview and brief cognitive testing. This means that participation in the study does not involve risk of significant harm. Some participants might find that undergoing cognitive testing is irritating or unpleasant. In such cases the researcher will treat the

participant sensitively, offering to stop testing or to give the participant a break before resuming later, as appropriate.

The benefits of involvement are that any potential cases of delirium and/or cognitive impairment will be brought to the attention of the clinical team. The research team will not be providing a clinical diagnosis but will provide findings from the cognitive testing and interview which could prompt a clinical assessment leading to a diagnosis. This could be a significant benefit to the patient in that it could lead to enhanced care if the delirium or cognitive impairment had not been detected in clinical assessments conducted before the research assessments.

4.6 Participant Withdrawal

Participants will have the right to withdraw at any point.

5. SAFETY

This is an observational study involving bedside interview and brief cognitive testing. There are no invasive procedures. Thus there are no significant safety concerns with respect to the methods used in the study, because these methods could not directly result in significant harm. Therefore, no adverse events or serious adverse events will be recorded on the CRF or reported to the sponsor.

It is important to note that patients in the study will all be emergency admissions, and potentially could deteriorate rapidly. This could happen during the cognitive testing. However, the cognitive testing is being done by staff nurses who are qualified to recognise any such deterioration and immediately bring this to the attention of the clinical team.

6. DATA COLLECTION

The experimental assessments of delirium will be the 4AT and the CAM. 4AT data will be used for the primary objective as a binary outcomes, with 0-3 scores giving a 'no delirium' classification, and 4-12 scores giving a 'delirium' classification; for the secondary objectives, continuous scoring, from 0-12, will be studied as a possible severity indicator, and scores of 1-3 (indicating cognitive impairment but not delirium) can be studied against other assessments of chronic cognitive impairment). The scores of items 1 and 4 of the 4AT can be scored as either 0 or 1, and items 2 and 3 as 0, 1, or 2. The CAM will scored as delirium present or absent according to the algorithm. The 4AT and the CAM scoring will be recorded on a paper Case Record Form.

The reference standard main assessments are as detailed in Section 3 above. All data will be recorded on a paper Case Record Form B. We will also collect standard demographic variables in Case Record Form.

For the criterion validity and economic analysis from medical records we will examine length of stay, adverse events such as falls, institutionalisation, and mortality up to 12 weeks. These data will be recorded on Case Record Form.

Patient resource-use will be derived from medical records, including the 'TrakCare' (InterSystems Corporation, Cambridge, MA, USA) electronic patient record system, where available, as well as via patient or carer self-report. The self-report resource-use questionnaire will include questions regarding patient health and social care utilisation with a maximum recall period of 16 weeks. The self-report resource use questionnaire will be developed specifically for the study for use by patient or proxy-respondent using guidance from the Database of Instruments for Resource Use Measurement[46]. Administration of the questionnaire will be conducted at 12 weeks by one of the researchers in the study team, face-to-face where patients are still hospitalised, or via telephone. Data from the questionnaire will be recorded on Case Record Form C.

The data on all the Case Record Forms will be transcribed into a secure database by the researchers or a suitably qualified member of the research team. This will conducted using Edinburgh Clinical Trials Unit Standard Operating Procedures. Quality checking will be performed in 10% of Case Record Forms.

7. STUDY OVERSIGHT

Study oversight is through the Trial Steering Committee, which will meet every four months during the study. The Trial Steering Committee comprises two lay representatives, three independent experts (one of whom is the Chair of the Committee), the PI, the study statistician, and representatives from the Edinburgh Clinical Trials Unit.

8. STATISTICS AND DATA ANALYSIS

8.1 Randomisation

The allocation sequence will be created using computer-generated random numbers. Participants will be randomised in a 1:1 ratio to be assessed using the 4AT or CAM experimental assessment. The order in which they receive the reference standard and experimental assessment will also be randomised in a 1:1 ratio. Randomisation will be stratified by study site with block allocation. The randomised allocations will be concealed until they are assigned as the randomisation system will be web-based and require a personal log-in and password. Once randomisation has been performed neither the researchers nor the participant will be blinded to the allocation as both will be aware of the assessments conducted and the order in which they are performed.

8.2 Sample Size

Sample size calculation: 450 patients will be randomised to assessment by 4AT and 450 to CAM. We will recruit sufficient patients to account for attrition; though we do not expect significant attrition because the recruitment, consenting and assessment process takes place over a small number of hours, in a single episode. Of the 450 patients within each assessment arm, 15% (67) would be expected to have delirium. The specificity of the triage tool would be estimated based on the 85% (383) without delirium, while the sensitivity would be estimated from the 67 with delirium. Based on analysis using the normal approximation to the binomial distribution, the two-sided 95% confidence interval widths for the specificity and sensitivity would be as shown in the table for a range of levels of diagnostic test performance.

Table 1 Precision of specificity, sensitivity estimation

Parameter	Relevant sample size	True level of parameter	95% confidence interval width
Specificity	383	0.5	± 0.050
Specificity	383	0.7	± 0.046
Specificity	383	0.9	± 0.030
Sensitivity	67	0.5	± 0.120
Sensitivity	67	0.7	± 0.110
Sensitivity	67	0.9	± 0.072

It will therefore be possible to estimate the specificity precisely and the sensitivity with moderate precision. The precision in estimating negative predictive value would be expected to be similar to that for specificity; for positive predictive value it would be expected to be similar to that for sensitivity. For the secondary objective of comparing 4AT and CAM, based on analysis by continuity corrected chi-squared test, we have 83% power to detect a difference in specificity of 0.1, assuming a null hypothesis of specificity=0.70 for both tests and a 5% significance level. The corresponding difference detectable for sensitivity (null hypothesis sensitivity=0.7) would be 0.224 with 80% power.

8.3 Analyses

The analyses will be carried by the study statistician Dr Christopher Weir and colleagues. The statistical analysis plan will be agreed prior to database lock, and analyses conducted prior to code breaking.

Primary objective:
(a) 4AT vs reference standard: the diagnostic accuracy of 4AT versus the reference standard will be assessed using positive and negative predictive values, sensitivity and specificity. The exact binomial 95% confidence interval will be reported for each measure. An ROC curve will be constructed to verify that the proposed cut point on the 4AT score is appropriate. The area under the ROC curve and its 95% confidence interval will be reported.

Secondary objectives:
(a) 4AT vs CAM: differences in each of sensitivity, specificity, positive and negative predictive values between 4AT and CAM will be tested by Fisher's exact test and quantified by the difference in the two proportions (4AT-CAM) and its 95% confidence interval. To aid comparison of 4AT and CAM, the overall performance of each will also be summarised using Youden's Index (sensitivity minus false positive rate) and the odds ratio of sensitivity to specificity.
(b) Performance of the 4AT cognitive screening items: is the 4AT an adequately sensitive tool for detecting general cognitive impairment as judged against a documented history of dementia and/or the Informant Questionnaire for Cognitive Decline in the Elderly? Methods as per primary objective.
(c) 4AT vs clinical outcomes: as assessment of criterion validity, we will assess the performance of the 4AT in predicting length of stay, institutionalisation, and mortality, up to 12 weeks. Descriptive statistics of clinical outcomes (continuous variables: mean, median, standard deviation, minimum,

maximum; categorical variables, number and percentage of participants) will be presented for the groups with and without 4AT scores above the cut point of 3.
(d) We will conduct analyses examining performance of individual items of the 4AT, e.g. is altered level of alertness alone a good predictor of delirium diagnosis? (Methods as per primary objective);
(e) We will assess the 4AT total score as a measure of delirium severity by calculating the Spearman correlations between 4AT and DRS-R98 scores and its 95% confidence interval.
(f) Health Economic Component (see below):

Full details of the proposed statistical analyses for Objectives (a) to (e) will be documented in a statistical analysis plan (SAP) which will include details of methods for calculating derived variables, methods for handling missing data and withdrawals, any sensitivity analyses and approaches to testing the assumptions in the statistical analyses. The SAP will outline the plan for validation of the statistical analysis. The SAP will be finalised prior to the locking of the trial database and will be prepared by individuals blinded to the randomised allocations**.**

Health Economic Component: generalised linear models will be used to analyse 12 week cumulative costs. A Bayesian microsimulation decision model will be developed to estimate delivery costs associated with the patient pathway as a function of the sensitivity and specificity of the triage tool and subsequent resource consequences. Potential consequences may include additional diagnostic procedures (e.g. more detailed cognitive screening and brain imaging), altered management as well as re-admissions. The decision analytic model will be conceptualised, developed and disseminated in accordance with the recent recommendations of good practice by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making[47]. Key model input parameters will be derived from the prospectively collected data as part of the study as well as recent systematic reviews within the existing literature. Although evidence synthesis methods for health technology assessments have been published, meta-analytic techniques will be needed to ensure robust model parameter estimates. The meta-analysis will take the form of a bivariate random effects model in order to account for the correlation between sensitivity and specificity within diagnostic tools[48].

The meta-analysis and decision model will be estimated simultaneously within a Bayesian framework[49,50], using R and C++ programming languages as well as the Just Another Gibbs Sampler (rJAGS) R package. An intuitive appeal of this approach, as outlined by Novielli et al.[51], ensures that a probabilistic sensitivity analysis can be undertaken without the need for any re-parameterisation of the meta-analytic parameter estimates and for ease in dissemination to policy makers. The prior distribution for the Bayesian decision model to evaluate the 4AT will be formulated as an empirical prior derived from the existing evidence on the CAM. Sensitivity analysis of this prior distributional assumption will be explored and presented to aid decision-making on the resource-consequences of the 4AT and CAM over an initial 4 week period.

9. DATA PROTECTION

9.1 Data Protection

Participant confidentiality will be respected at all times during this project. Data will be collected and handled in line with Edinburgh Clinical Trials Unit Standard Operating Procedures and in accordance with NHS Trust policies at each participating site. This will ensure systems are in place to protect confidentiality of participants and the systems are secure.

All electronic data will be link-anonymised. Published results will not contain any personal data that could allow identification of individual participants.

9.2 Data Storage

Data collected at sites will be recorded on paper CRFs which will be stored securely. These forms will be identified by participant number only - no identifiable information will be recorded on these forms. Any patient identifiable data (i.e. consent forms and contact details) will be securely stored in locked filing cabinets in locked offices in each of the study sites. Data from the paper CRFs will then be entered onto a secure database by the researchers at each site. Computers used to collate the data will have limited access measures via user names and passwords.

9.3 Data Archiving

All data collected in this study will be archived at sites as detailed in the sponsor's Standard Operating Procedure. The length of time the data will be retained will be for 10 years.

9.4 Confidentiality

All paper study documents will be securely stored in locked filing cabinets in locked offices in each of the study sites. Data stored electronically will be link-anonymised. The code linking the anonymous identifier used in the studies and the patient details will be stored securely and separately from the study databases.

10. Data access and quality assurance

The security of all data will be maintained by storage on a secure University network, accessible only by the key researchers and responsible members of the study team.

Select members of the research team including (a) designated Edinburgh Clinical Trials Unit staff and (b) members of the clinical research team who require to process the forms will have access to personal data including names, addresses, phone numbers and email addresses in order to undertake the

questionnaire follow-up. In addition to this, access to hard copies of the CRF and questionnaire data will be required for study monitoring and audit purposes.

The study database resides on the Edinburgh Clinical Trial Unit's in house data management system. The system uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS. Access to the system is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data. The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is required.

11. Dissemination

Conference presentations: We will present the findings widely. We will cover the main conferences in the field. We will seek to present the work to the relevant professional groups: acute medicine, acute nursing, emergency medicine (doctors and nurses), geriatrics, and liaison psychiatry. The conferences could include: British Geriatrics Society, Society for Acute Medicine, Scientific Conference of the College of Emergency Medicine, Symposia at Royal Colleges, European Delirium Association, European Association of Psychosomatic Medicine, American Geriatrics Society and the American Delirium Society. We will submit a presentation to the INVOLVE conference led by our service user advisory group. Authorship will comprise the 4AT study team with additional input from staff employed on the project and/or others asked to contribute.

Publications: We will seek to submit the major findings in paper a major general journal such as the British Medical Journal or Annals of Internal Medicine. Supplementary findings will be submitted to high quality international peer-reviewed journals. Authorship will be as per Conference Presentations.

Website: The 4AT website (www.4AT.com) has received >35000 visits since it was launched in June 2011. We will use www.the4AT.com as the basis for an expanded website which will provide the 4AT and instructions. The website will also ultimately provide access to summaries of validation data. The website will be in a format accessible to multi-disciplinary staff and in addition to patients and families. We will seek to have links to the 4AT website from key external websites.

NICE guidance: This proposal was developed to address a research priority identified in NICE guidance. We anticipate that the findings will influence future NICE recommendations for identification of delirium. This will ensure that the findings of this project are disseminated and influence practice.

Knowledge mobilisation in the NHS: We will seek to encourage transfer and implementation of the research findings into practice through system-wide contact with policy-makers and practitioners, and follow-on research and audit projects. System-wide contact will be carried out through professional clinical organisations and professional managerial organisations. We will implement the 4AT into delirium care bundles in our centres and assess adherence to use of the 4AT, and then disseminate this 'real world' impact through all the above channels.

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NHS Lothian

APPENDIX 1

Sub study 1 outline

An exploration of friend and relative experience using the emotional touchpoints tool: investigating experience, knowledge and understanding of delirium

Background

The parent study - *Development and validation of the 4AT: a new rapid screening tool for delirium* - is assessing the diagnostic accuracy of the 4AT and Confusion Assessment Method (CAM) versus the reference standard of a DSM IV diagnosis. An aspect of this study involves inviting and consenting close friends or family to complete the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE). This qualitative sub-study seeks to further explore the experiences of close friends or relatives with specific reference to delirium.

The current lack of robust clinical detection and diagnosis of delirium is associated with poor patient outcomes (Anand & MacLullich[1]; NICE[2]) and by extension can lead to challenging experiences for close friends and families. Initial research prior to the parent study showed that knowledge and understanding of delirium is limited amongst healthcare professionals whose very role it is to provide information and support to patients, friends and relatives (Bellilli *et al*[3]). A recent study suggests that the experience of delirium can be bewildering for friends and family, and lead to a lack of understanding and misconceptions surrounding the condition (Day & Higgins[4]).

Improving delirium care necessitates development of clinical expertise, yet we must also be attentive to the experiences, beliefs and perceptions related to delirium amongst close friends and family (Dewar *et al*[5]). These individuals are ostensibly the primary care givers and are present throughout the patient's journey. They are key to providing accurate and authentic information to aid clinical diagnosis and may be the only constant source of support post-discharge. Any beliefs and concerns they hold regarding delirium are likely to inform a wider public awareness of the condition. This sub study will determine the experience, knowledge and understanding of delirium from friends and relatives perspectives. We anticipate the views and experiences of these participants will provide a rich source of data and contribute to the limited literature base in this area. Our findings will help identify ways to engage and support close friends and families of patients with delirium.

Study objectives and endpoints

To collect, collate and contextualise rich data concerning relative/friend experiences, knowledge and understanding of delirium.

Research Methods

This sub study will utilise a qualitative approach. Research assessments in the parent study will lead to a delirium positive or negative ascertainment. The close friends or relatives of patients receiving a delirium positive ascertainment will be approached to participate in the sub study. The primary research methodology of qualitative enquiry will be employed through use of the Emotional Touchpoints tool (Dewar *et al*[6]). The tool is recommended by NHS Lothian as a method of eliciting stories from patients, relatives and staff. It is recognized that the tool helps to foster an emotionally rich vocabulary when discussing experiences. Three or four touchpoints will be chosen by participants such as 'visiting friends/family in hospital' or 'talking to nurses and doctors'. Each participant will then choose from a selection of positive and negative emotional words to help describe each touchpoint. Interviews will be recorded and transcribed as a participant story. Participants will approve their participant story to confirm accuracy and will be able to edit if applicable. An analytical framework will be developed to assist with theme generation. Transcripts will be read multiple times in order to develop relevant codes and analytical themes.

Study population

10 participants (only 1friend/relative per patient enrolled in parent study) recruited from within NHS Lothian

Inclusion criteria

- friend/relative of patient enrolled in parent study who has been ascertained as delirium positive
- 18 years of age or over
- available for interview, during working hours, in the Edinburgh area

Exclusion criteria

- unfamiliar with relative's condition and current hospital admission
- unable to give informed consent
- unable to communicate in English

Study design

- potential participant identified and approached with details of sub study
- contact details sought if willing to participate
- contacted to arrange time and location of interview
- a single data collection visit lasting approximately an hour
- following informed consent process, participant will be invited to discuss experience, knowledge and understanding of patient's condition using specific topics and a selection of descriptive words to aid discussion
- recorded interview will take place at a prearranged venue of convenience to participant eg. hospital interview room / participant's home

- participant will be provided with a copy of interview story transcript for verification/editing either in person at a subsequent hospital visit or via post / email
- participants will be provided with final published results of sub study if requested

Recruitment and consenting process

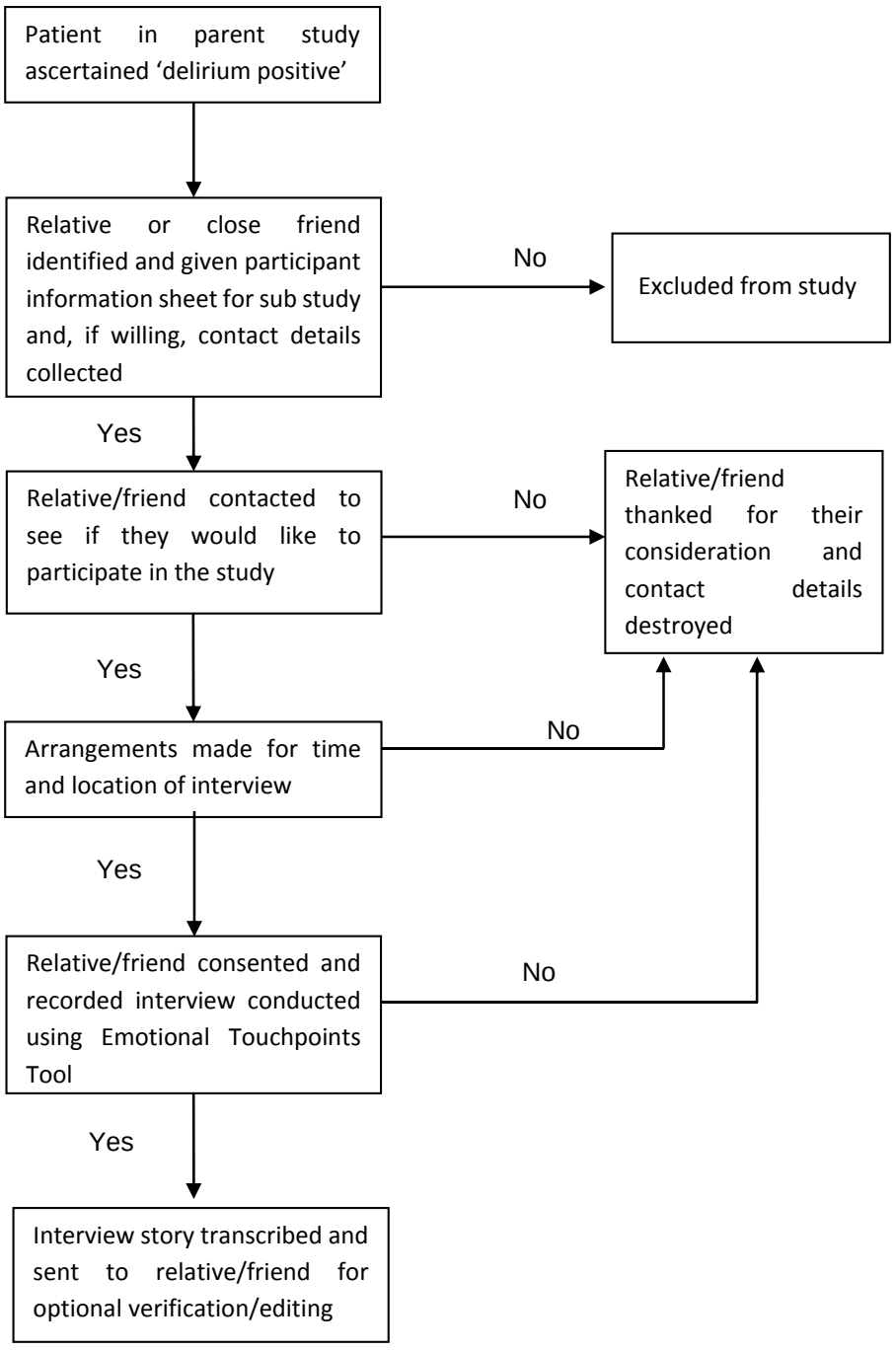
This sub study will aim to recruit ten participants at the Royal Infirmary of Edinburgh site only. Potential participants will be identified as the close friends or relatives of patients with ascertained delirium in the parent study. These close friends or relatives will be familiar with the patients' relevant condition and hospital admission. The ascertainment of delirium is confirmed by research assessments completed as part of the parent study. Close friends or family of patients in the parent study will ideally have previously consented to providing an IQCODE. An opportunity will be offered to take part in this sub study. We will aim to recruit only one friend/relative per delirium positive patient who would be available for interview during working hours in the Edinburgh area.

The initial approach will take place in person, during a hospital visit, following patient assessments for the parent study. After reading the information sheet, participants will be asked if they would be happy to be contacted by phone or e-mail in the next few days to discuss taking part in the interview sub study, and if so to arrange a suitable time for the interview to take place. They will be given at least twenty four hours to consider the information sheet before being contacted. Receipt of contact details will give implied consent for research staff to contact potential participants. Those agreeing to take part in the study will then be contacted again prior to the interview to see if they are still happy to take part. Participant informed consent will be gained prior to the interview commencing. The contact details of those who do not wish to take part will not be retained. This information will be anonymised and recorded on a screening log.

Study procedures

Consenting participants will be interviewed at a suitable location, at a time convenient to each individual. Emotional Touchpoint interviews surrounding their experience, knowledge and understanding of delirium will be conducted and audio recorded. Participants will be contacted and given the option to verify/edit transcripts of their story soon after interview completion. If there is no response to this contact, data will be retained and used for analysis.

Flowchart Showing Sub Study Process



Description of analysis

- Interview story transcripts will be read, re-read and coded separately by two researchers to identify themes
- Researchers will compare and contrast separately coded transcripts to reach a consensus agreement on major themes and any sub-themes
- Quotes from transcripts will be selected to illustrate themes and usefully present results

Data management

All data will be gathered, stored, and transferred in a manner which is safe, ensures accuracy and maintains participant confidentiality yet remains accessible to research staff. Data will be anonymised as soon as is practicable, and electronic devices used for data collection will have appropriate security settings enabled to prevent unauthorised access. Identifiable participant details will be held separately in a secure filing cabinet.

All electronic data collected for the study will be stored in a designated shared drive. The data folder will only be accessible to the research team. Data stored on external media (e.g. audio digital recorders, pen drives) will be transferred to the relevant shared folder as soon as practicable. After 5 years the audio recordings will be destroyed.

All hard copy data will be stored in a locked filing cabinet in a secure office. Under no circumstances will paper records be left unattended in a public area with anyone outside the research team.

Safety

This is a participant-led interview study. There are no invasive procedures. Thus, there are no significant safety concerns with respect to the methods used. Therefore, no adverse events or serious adverse events will be recorded or reported to the sponsor.

The study will be conducted with adherence to the relevant ACCORD Standard Operating Procedures (SOP) on serious breaches of GCP (SOP CR003) and on identifying and reporting deviations and violations (SOP CR010).

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