STUDY PROTOCOL

Validation of the 4AT tool for delirium assessment in specialist palliative care settings: protocol of a prospective diagnostic test accuracy study [version 1; peer review: awaiting peer review]

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Abstract

Background: Delirium is a serious and distressing neuropsychiatric condition, which is prevalent across all palliative care settings. Hypoactive delirium is particularly common, but difficult to recognize, partly due to overlapping symptoms with depression and dementia. Delirium screening tools can lead to earlier identification and hence better management of patients. The 4AT (4 'A's Test) is a brief tool for delirium detection, designed for use in clinical practice. It has been validated in 17 studies in over 3,700 patients. The test is currently used in specialist palliative care units, but has not been validated in this setting. The aim of the study is to determine the diagnostic accuracy of the 4AT for delirium detection against a reference standard, in hospice inpatients.

Methods: 240 participants will be recruited from the inpatient units of two hospices in Scotland. If a patient lacks capacity to consent, agreement will be sought from a legal proxy. Each participant will complete the 4AT and a reference standard assessment based on the diagnostic delirium criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This will be supplemented by tests of cognition and attention, including reverse days of the week, counting down from 20 to 1, Vigilance 'A', the Observational Scale for Level of Arousal, the modified Richmond Agitation Sedation Scale and the Delirium Rating Scale-Revised-98. The assessments will be conducted in a randomized order by two independent clinicians, who will be blinded to the results until both are complete. Primary outcomes will be the sensitivity and specificity of the 4AT in detecting delirium.
Discussion: The findings will inform clinical practice regarding delirium assessment in palliative care settings.

Trial registration: ISRCTN ISRCTN97417474 (21/02/2020).

Keywords
4AT, 4 'A's Test, delirium, screening, detection, hospice, specialist palliative care, palliative care, DSM-5

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Competing interests: AMJM led the design of the 4AT in 2011.

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Plain language summary

Delirium is a serious and distressing condition, which commonly affects people with terminal illness. Approximately a third of patients will have delirium on admission to hospices. Delirium usually develops over hours to days. It can cause confusion, and problems with memory, concentration, perception (may develop hallucinations) and altered consciousness (people can become agitated or drowsy and withdrawn). It is important to diagnose delirium early, as it increases the person’s chance of recovery. When a person has only hours or days to live, their delirium is less likely reversible, but early detection is still beneficial, as it helps healthcare professionals decide how they can best support the person and their family.

The 4 ‘A’s test or 4AT is a short, easy to administer bedside test, used by healthcare professionals to determine if patients may have delirium. Research has shown the 4AT to be an effective test in hospital patients. It is currently used in hospices, but research is needed to review its use in this setting. This article describes the proposed study to examine the effectiveness of the 4AT in detecting delirium in terminally ill hospice patients.

Patients admitted to two hospices in Scotland will be invited to take part in the study. Those participating in the study will undergo two assessments - the 4AT and another more detailed delirium assessment.

This study will provide evidence about the accuracy of the 4AT in detecting delirium in terminally ill hospice patients. If the study shows the 4AT to be effective, it may be more readily used in routine practice, than other more complex and lengthy delirium tests. If delirium is detected earlier, it may lead to better care for these patients and their families.

Abbreviations

- DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
- DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition
- DSM-III: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised
- CAM: Confusion Assessment Method
- bCAM: Brief Confusion Assessment Method
- 4AT: 4 ‘A’s test
- SQiD: Single Question in Delirium
- NuDESC: Nursing Delirium Screening Scale
- DOS: Delirium Observation Scale
- DRS: Delirium Rating Scale
- DRS-R-98: Delirium Rating Scale Revised 98
- MDAS: Memorial Delirium Assessment Scale
- AMT-4: Abbreviated Mental Test -4
- CCC: Concordance Correlation Coefficient
- ACCORD: Academic and Clinical Central Office for Research and Development

Background

Delirium is a serious and distressing neuropsychiatric condition, characterized by an acute disturbance in attention, awareness and cognition. Delirium severity may fluctuate throughout the day, and be associated with disturbances in the sleep-wake cycle. Cognitive changes may impact memory, orientation, language, visuospatial ability and perception. Delirium can be highly distressing for patients and their families and is associated with poor outcomes.\(^5\).

Delirium is extremely common across all palliative care settings. A recent systematic review estimated the median (range) point prevalence of delirium on admission to palliative care inpatient settings as 32% (6.6%–73%) and period prevalence prior to death as 75% (58%–88%).\(^5\) Hypoactive delirium is more common than other subtypes in palliative care\(^5\) but may be less noticeable and go under-recognised due to overlapping symptoms with depression, dementia and fatigue.\(^1\–^3\).

International guidance recommends routine assessment for risk factors of delirium on admission to hospital and other care settings, and subsequently if there are any fluctuations or changes in behaviour or cognition.\(^1\–^6\) Delirium assessment tools are recommended and may lead to earlier detection. Improved detection may lead to better management, including investigation and treatment of the underlying cause and/or better symptom control, resulting in more favourable outcomes for both patients and their families.

Delirium tools are available for different purposes:\(^8\):

- for delirium detection at first presentation, and at other times when delirium is first suspected: the Confusion Assessment Method (CAM)\(^20\), shorter versions, including the brief Confusion Assessment Method (bCAM)\(^21\), the 4 ‘A’s test (4AT)\(^22\) and informant screening tools, such as the Single Question in Delirium (SQiD)\(^23\).

- for monitoring of new onset delirium in inpatients, on a regular basis, daily or more frequently: the Nursing Delirium Screening Scale (NuDESC)\(^24\) and Delirium Observation Scale (DOS)\(^25\).

- as research assessments: The Delirium Rating Scale (DRS) and the Delirium Rating Scale Revised-98 (DRS-R-98)\(^26\).

Table 1 shows examples of validation studies in palliative care and oncology populations.
### Table 1. Validation studies of Delirium assessment tools used in palliative care and oncology populations²²⁻²⁹

<table>
<thead>
<tr>
<th>Assessment tool</th>
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<th>Study description</th>
<th>Results</th>
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<tr>
<td>Memorial Delirium Assessment Scale (MDAS)²⁰</td>
<td>33 Hospitalised cancer and AIDS patients (Breitbart, 1997)²⁰</td>
<td>MDAS compared to DSM-III and DSM-IV delirium diagnosis</td>
<td>Sensitivity 0.71, Specificity 0.94 (cut-off score 13)</td>
<td>The MDAS is a brief, reliable tool for assessing delirium severity among medical inpatients. It may also be useful in delirium diagnosis.</td>
</tr>
<tr>
<td></td>
<td>51 Hospitalised cancer and AIDS patients (Breitbart, 1997)²⁰</td>
<td>MDAS compared to Delirium Rating Scale (DRS) and Clinician’s Global Rating of Delirium Severity</td>
<td>There was high correlation between MDAS scores and the alternative measures of delirium: DRS ($r = 0.88$, $p &lt; 0.0001$) and Clinician’s Global Rating of Delirium Severity ($r = 0.89$, $P &lt; 0.0001$).</td>
<td>The MDAS is a valid and reliable tool for delirium diagnosis and severity monitoring. Proration of MDAS total scores was required in approximately a fifth of delirious patients. This may limit the use of MDAS in research, but be useful in clinical practice.</td>
</tr>
<tr>
<td></td>
<td>104 Palliative care inpatients (advanced cancer) underwent 330 assessments (Lawlor, 2000)²¹</td>
<td>MDAS compared to DSM-IV diagnosis</td>
<td>Sensitivity 0.97, Specificity 0.95 (cutoff score 7)</td>
<td>The MDAS is a valid and reliable tool for delirium diagnosis and severity monitoring. Proration of MDAS total scores was required in approximately a fifth of delirious patients. This may limit the use of MDAS in research, but be useful in clinical practice.</td>
</tr>
<tr>
<td></td>
<td>77 Palliative care unit inpatients (O’Sullivan, 2015)²¹</td>
<td>MDAS compared to DRS-R-98 in patients with DSM-IV diagnosed delirium</td>
<td>Concordance correlation coefficient (CCC)=0.70</td>
<td>There was substantial overall agreement in the severity scores of the MDAS and DRS-R-98 in palliative care inpatients.</td>
</tr>
</tbody>
</table>
| Confusion Assessment Method (CAM)²⁰                  | Pilot study with 32 patients, followed by main study with 52 Palliative care inpatients (Ryan, 2009)²³ | CAM compared to DSM-IV diagnosis                                               | Pilot study: Sensitivity 0.5, specificity 1.0.  
Main study (assessors received more training of CAM than in pilot study): Sensitivity 0.88, Specificity 1.0 | The CAM is a valid screening tool in palliative care inpatients, but accuracy depends on assessors’ training in its use.                            |
<p>|                                                       | 21 Oncology inpatients (Sands, 2010)²³ | CAM compared to Psychiatrist interview                                            | Sensitivity 0.4, Specificity 0.92.                                      | Primary focus of this study was the SQID. The CAM performed poorly, likely because the assessors had limited training in its use.                     |
| Brief/short Confusion Assessment Method²¹           | 51 Palliative care inpatients (Rainsford, 2014)²³ | Short CAM compared to DRS-R-98 and clinical judgement                           | Incidence of delirium was 29% based on clinical judgement alone, but increased to 43% when validated assessment tools (CAM and/or DRS-R-98) were used. | The study supports the short CAM as an appropriate screening tool. The DRS-R-98 is limited as a screening tool by its complexity and time taken to administer. |
|                                                       | 36 Palliative care unit inpatients or other inpatients reviewed by palliative care team (Wilson, 2019)²³ | Brief CAM compared to DSM-5 diagnosis                                          | Sensitivity 0.80, Specificity 0.87                                     | The brief CAM was found to have good sensitivity and specificity in veteran palliative care inpatients, but further validation studies with larger sample size are needed. |
| Nursing Delirium Screening Scale (Nu-DESC)²⁴        | 59 assessments of 52 haematology-oncology and internal medicine inpatients (Gaudreau, 2005)²⁴ | Nu-DESC compared to CAM                                                         | Sensitivity 0.86, Specificity 0.87                                     | The Nu-DESC, a brief, easy to use tool, demonstrated high diagnostic accuracy in oncology inpatients, but further studies with larger sample size are required. |
|                                                       | 43 Palliative care unit inpatients, (Barnes, 2019)²⁵ | Nu-DESC compared to MDAS                                                      | There was positive correlation between the 24 hour maximum and mean Nu-DESC scores and the MDAS ($r=0.41$, $p=0.006$, and $r=0.40$, $p=0.008$ respectively), but lower or insignificant correlation when Nu-DESC scores using items 2-4 were used. | The Nu-DESC may be useful to monitor delirium severity in palliative care inpatients.                                                                 |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>Delirium Observation Screening Scale (DOS)</td>
<td>48 palliative care unit inpatients (Detoyer, 2014)</td>
<td>DOS compared to CAM</td>
<td>Sensitivity 0.82, Specificity 0.96</td>
<td>The DOS can be used as a screening tool in ‘verbally active’ palliative care inpatients. Further validation studies are required.</td>
</tr>
<tr>
<td></td>
<td>78 assessments of home hospice patients (Jorgensen, 2016)</td>
<td>DOS compared to CAM</td>
<td>Sensitivity 0.97, Specificity 0.89</td>
<td>The DOS is a useful observational screening tool in home hospice patients. It is quick to learn and cognitive testing is not required. Further validation studies are required.</td>
</tr>
<tr>
<td></td>
<td>187 oncology inpatients (Neefjes, 2019)</td>
<td>DOS compared to CAM</td>
<td>Sensitivity &gt;0.99, Specificity &gt;0.99</td>
<td>The DOS is a brief, accurate screening tool in patients with advanced cancer.</td>
</tr>
<tr>
<td>Single Question to identify Delirium (SQiD)</td>
<td>21 oncology inpatients (Sands, 2010)</td>
<td>SQiD and CAM were compared to Psychiatrist interview</td>
<td>SQiD: Sensitivity 0.8, Specificity 0.71, CAM: Sensitivity 0.4, Specificity 0.92</td>
<td>The SQiD is a quick and easy to use tool, which can be incorporated into the admission process. If the SQiD scores positive, this could trigger a more detailed assessment for delirium. The CAM performed poorly in this study, likely because the assessors had limited training in its use.</td>
</tr>
<tr>
<td></td>
<td>4 ‘A’s test (4AT)</td>
<td>None</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Delirium Rating Scale- revised-98 (DRS-R-98) and Delirium Rating Scale (DRS)</td>
<td>Used as reference standard delirium assessments in research studies</td>
<td></td>
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</table>

The DRS-R-98, a clinician-rated 16-item scale with 3 diagnostic and 13 severity scales, is able to distinguish reliably from depression and dementia. Use in clinical practice is limited because of training required prior to use and time taken to administer (at least 20–30 minutes with the patient, plus additional time to gather informant history and review case notes).

The Memorial Delirium Assessment Scale (MDAS), a 10-item scale, used for delirium detection and severity monitoring, takes approximately 10 minutes with the patient, plus additional time to gather informant history. It has a simpler format and is easier to rate than the DRS-R-98, but still requires moderate training to administer. A study in a palliative care inpatient unit demonstrated 97% sensitivity and 95% specificity (cutoff score = 7).

The CAM and its shorter variants are quicker to administer than either the MDAS or DRS-R-98 (approximately 5–10 minutes), but still require moderate training prior to use, as well as additional cognitive testing. Aspects requiring subjective judgement by the assessor can be more complex and time-consuming to rate, plus there is limited advice for scoring non-verbalizing patients. This may account for high levels of sensitivity and specificity in some studies, but lower results when scored by those less experienced.

The informant tool, the Single Question in Delirium (SQiD), which asks ‘Do you feel that (patient’s name) has been more confused lately?’, has been validated in oncology patients (80% sensitivity and 71% specificity), but not in palliative care patients. Use of the SQiD is limited when an informant is unavailable.

The 4 ‘A’s Test (4AT) is a short bedside test for detecting delirium, for use in clinical practice. It takes a few minutes to complete and incorporates 4 items: (1.) An observational measure of alertness, (2.) The Abbreviated Mental Test-4 (AMT4), (3.) The Months of the Year Backwards test, and (4.) Evidence of significant change or fluctuation in alertness, cognition or other mental function arising over the last 2 weeks and still evident in the last 24 hours. The first 3 items are assessed at the patient’s bedside. The last item is derived directly by the assessor or from informant history (i.e. taken from case notes, clinical staff or a relative or carer). The 4AT can be used by any healthcare professional, either at first contact or when delirium is suspected. It is one of the most frequently used delirium detection tools.
validated delirium tools in the literature. A recent systematic review and meta-analysis of 17 studies involving 3702 older adults in medicine, surgery, emergency and care home settings, demonstrated a pooled sensitivity of 88% and pooled specificity of 88%\textsuperscript{49}. The 4AT’s advantages over other tools are that no special training is required prior to use, and it is quick and easy to administer. Furthermore, all patients can be assessed, including those unable to communicate (patients with severe drowsiness or agitation.)

The 4AT is recommended for identifying patients with delirium\textsuperscript{14}, and is currently used in palliative care settings\textsuperscript{31–43}, but has not been validated for delirium screening in a terminally ill population.

**Study objective**
The study objective is to determine whether the 4AT is a valid tool for delirium detection in specialist palliative care settings. The diagnostic accuracy of the 4AT will be compared against a reference standard delirium assessment, based on the diagnostic criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Table 2).\textsuperscript{1}

**Methods**

**Study overview**
In developing this protocol, we drew on the study design and procedures of a previous 4AT validation study conducted in emergency departments and acute medical wards\textsuperscript{49}. This study is a prospective diagnostic accuracy study of the 4AT in a representative sample of hospice inpatients. Each participant will independently complete the 4AT and the reference standard delirium assessment based on DSM-5 criteria. Study procedures are described in Figure 1.

**Setting**
The study will take place at two hospices in Scotland. The hospices have 17 and 24 inpatient beds, respectively, and admitted a combined total of 700 patients in 2019. Patients with advanced progressive or incurable disease are admitted for complex end of life care, or because they have uncontrolled pain and/or other complex physical or psychological issues, that cannot be managed in other care settings.

**Participants and sample size**
Participants admitted acutely to the hospices will be included if they are aged 18 years or over. Patients will be excluded if they are comatose, unable to communicate in English, are severely dysphasic or have a combined severe hearing and visual impairment, which would limit participation in the study’s tests. Patients will also be excluded if there is a high level of patient and family distress, as judged by the clinical team, or the patient has an acute life-threatening illness requiring time-critical intervention (e.g. suspected spinal cord compression).

A recent meta-analysis of 17 studies on the diagnostic accuracy of the 4AT in a variety of clinical settings, reported a pooled sensitivity of 0.88 (95% CI 0.80-0.93) and a pooled specificity of 0.88 (95% CI 0.82-0.92)\textsuperscript{14}. In line with guidance described by Flahault et al. (2005)\textsuperscript{44} which suggests a sample size of 176, given a sensitivity/specificity of 0.85, and a minimal acceptable lower confidence level of 0.75, we plan to recruit 240 patients from the inpatient units across both hospices. We estimate that 80% of those recruited will complete the assessments, allowing data analysis on at least 200, slightly above the 176 needed.

**Screening**
Eligibility screening will take place every morning, and opportunistically, if practical, throughout the working day, as new patients are admitted to the hospice inpatient units. The clinical care team will identify potentially eligible participants by considering a checklist with the inclusion and exclusion criteria, as shown in Table 3. For patients screened as ineligible, age and reason for ineligibility will be recorded. If the reason for not approaching the patient later resolves (e.g. high level of patient and/or family distress or acute life-threatening illness requiring time-critical intervention), the patient may be approached on another occasion.

<table>
<thead>
<tr>
<th><strong>Table 2. Delirium diagnostic criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)</strong>\textsuperscript{1}.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong> A disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).</td>
</tr>
<tr>
<td><strong>B.</strong> The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.</td>
</tr>
<tr>
<td><strong>C.</strong> An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).</td>
</tr>
<tr>
<td><strong>D.</strong> The disturbances in Criteria A and C are not better explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma</td>
</tr>
<tr>
<td><strong>E.</strong> There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.</td>
</tr>
</tbody>
</table>

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (Copyright 2013). American Psychiatric Association. All Rights Reserved.
The direct clinical care team will identify potentially eligible participants, by reviewing the inpatient bed occupancy list every morning. This may be repeated at other times during the day, as practical, following admissions to the unit.

The clinical team will consider if the patient meets the inclusion and exclusion criteria

A member of the clinical team approaches the participant to ask if a researcher can come to talk with them about the study

Excluded through ineligibility. Reason and age of patient recorded

Patient says yes

Patient drowsy or incapable of discussing study

Patient says no

Excluded

Capacity assessment by Assessor A*

Incapable of giving informed consent

Consent sought by Assessor A*

Consent denied

Consent granted

Excluded

Randomisation of order of 4AT and reference standard assessment

4AT conducted by Assessor B

Reference standard assessment conducted by Assessor A*

Reference standard assessment conducted by Assessor A*

4AT conducted by Assessor B

Inpatient unit clinical team informed of assessment results

Consent is sought via legal proxy by Assessor A*

Consent denied

Unavailable

Excluded

Key: *Assessor A (the individual conducting the capacity testing and consent process) will always perform the reference standard assessment.

Figure 1. Study overview flow chart (adapted from Shenkin et al. (2008))

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Recruitment processes for participants with and without capacity

Eligible patients will be approached by the clinical team and asked if they would like to hear more about the study. If agreeable, the clinical researcher will provide verbal and written information about the study and invite them to take part. As part of this discussion, the patient’s capacity to consent to participation in the study will be assessed. If the patient is assessed as lacking capacity to decide, their legal proxy will be approached. The legal proxy could be their Welfare Attorney, Guardian or nearest relative (this is the order in which they will be approached). They will be asked to consider the previously expressed views of the patient, and if they think the patient would have wanted to participate in the study. The Adults with Incapacity (Scotland) Act 2000 permits a legal proxy to consent on behalf of an adult with incapacity45.

Due to the nature of delirium, it is possible the participant’s capacity to consent may fluctuate. If participants with capacity continue with the assessments shortly after giving consent, they are unlikely to lose capacity within this short space of time. However, if there is a longer period between the capacity/consent process and assessments, 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 remain valid just prior to the assessments being completed. That is, 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. However, if the researcher becomes aware the previously competent participant has now lost capacity, the assessments will continue in view of their previous consent.

Participants are free to withdraw from the study at any time, or the researcher may withdraw a participant. The reason for their withdrawal will be documented, if available, and data collected up to that point, will be used.

Training of data collectors

The 4AT assessors are hospice inpatient nurses and doctors, who completed delirium training, either during preparation for the study and/or as part of their professional training. Prior to the study, the 4AT was routinely used on admission to the inpatient units, and at other times when delirium was suspected.

The reference standard assessors are also part of the clinical team. Prior to study recruitment, these assessors completed additional training in capacity assessment, obtaining consent and delirium assessment with a Post-Doctoral Research Fellow and psychologist (ZT) and the Chief Investigator (AMJM), to ensure competence. Good Clinical Practice was also completed.

Assessments

1. Index test

The 4AT takes a few minutes to complete and is described earlier in this protocol22.

2. Reference standard assessment

The reference standard assessment may take up to 20 minutes to complete and is based on the delirium diagnostic criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Table 2). The battery of tests assessing cognition and attention includes reverse days of the week, counting down from 20 to 1, Vigilance ‘A’49, the Observational Scale for Level of Arousal25, the modified Richmond Agitation Sedation Scale (the term ‘drowsy’ is used instead of ‘sedation’)38 and the Delirium Rating Scale-Revised-98 (DRS R-98)38. A diagnosis of dementia or learning disability will be recorded. The assessor will review the patient’s clinical records and speak with someone who knows the patient well, such as a member of the clinical team and/or relatives (with the patient’s consent).

Following the reference standard assessment, the participant will be grouped into one of four categories – delirium present, possible delirium, no delirium, or undetermined, as defined in another recent delirium study49 (Table 4).

Where there is uncertainty of the patient’s categorisation, the reference standard assessor will discuss these ‘challenging cases’ with an expert panel. This panel includes a Consultant in Palliative Medicine (JS) and the Chief Investigator, who is a
Table 4. Reference standard assessment grouping (adapted from Rutter et al. (2018)⁹).

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium present</td>
<td>All 5 of the DSM-5 delirium core diagnostic criteria are positive</td>
</tr>
<tr>
<td>Possible delirium</td>
<td>Some DSM-5 delirium diagnostic criteria are positive (i.e. some features of delirium are present), but not all, due to missing information (perhaps about the history of onset of symptoms).</td>
</tr>
<tr>
<td>No delirium present</td>
<td>The core criteria are negative for delirium.</td>
</tr>
<tr>
<td>Undetermined</td>
<td>Some, but not all, DSM-5 delirium criteria are positive. This usually represents a resolving or subsyndromal delirium.</td>
</tr>
</tbody>
</table>

Consultant in Medicine of the Elderly (AMJM). The panel will be blinded to the results of the 4AT, until the final categorisation of the reference standard assessment is complete.

Data collection
Each participant will complete the 4AT and a reference standard delirium assessment by two independent clinicians. The assessor, who conducted the capacity and consenting process, will always administer the reference standard assessment. Given the fluctuating nature of delirium, the two assessments will be completed within a maximum three-hour time period (target interval 15 minutes). During this period, there will be no communication about the participant between the two assessors, until both assessments are complete (other than to arrange the timing of assessments).

The order of the two assessments will be randomised in a 1:1 ratio. The randomisation allocation will occur immediately following recruitment. An administrator at each site, who is independent of the assessments, will use a block randomised list to direct the order of the assessments.

Once both assessments are complete, the outcome of the reference standard assessment will be communicated verbally to the clinical team looking after the patient, in accordance with the consent process. This is because a provisional research diagnosis of delirium may result in improved patient care.

Data recording, storage and monitoring
Data will be recorded on paper case report forms and kept securely in locked cabinets, in offices with limited access. Study data collection forms (4AT and reference standard assessment results etc.) will be identified by a participant’s unique identification (ID) number only, to maintain confidentiality. Records with the participant’s name and other personal identifiers (eligibility and recruitment logs, consent forms etc.) will be stored separately from data collection forms with the participant’s ID only.

Clinical researchers will transcribe the data on case report forms into secure databases within Marie Curie Cancer Care IT networks in Edinburgh and Glasgow. The databases will only be accessible to clinical researchers and the Research steering committee, who will be responsible for monitoring the data quality.

Data analysis
The diagnostic test accuracy of the 4AT for delirium detection in specialist palliative care inpatient populations, versus the reference standard, will be determined using sensitivity, specificity, and positive and negative predictive values. The exact binomial 95% confidence interval will be reported for each measure. A ROC curve analysis will be performed, and the area under the ROC curve and its 95% confidence interval will be reported. Analyses will be completed using IBM SPSS Statistics.

Participants with missing data from the 4AT and reference standard assessments will be included in the statistical analysis, if there is enough information to decide on categorisation. Cases with insufficient information will be excluded, and expert panel advice will be sought where there is uncertainty.

Data protection
Data will be collected, stored and handled in accordance with guidance from Marie Curie Research Governance committee, the sponsor ACCORD (the Academic and Clinical Central Office for Research and Development) and the NHS Scotland A Research Ethics Committee.

The principle investigator will have direct access to their own site’s data, and to the other site’s on request. To ensure confidentiality, the Research steering committee will only have access to data that has had identifiable participant information removed.

Personal data will be stored securely for a maximum of three years to allow full analysis of the data. Study documentation will not be destroyed without permission from the sponsor.

Study oversight
There is a process for reporting adverse events, however this is a relatively ‘low risk’ study - the assessors are trained palliative care nurses and doctors, and the study tests are already used in clinical practice. The sponsor, ACCORD, will be responsible for external oversight, which may involve monitoring and audit of study activity and documentation.

Study status
Recruitment commenced in October 2019. We initially anticipated that recruitment would run for up to 15 months, however recruitment was temporarily stopped in March 2020 due to the coronavirus disease 2019 (COVID-19) pandemic. Recruitment
will resume as soon as permitted, in line with research and clinical governance requirements.

Dissemination of information

The anonymised data will be shared on the ISRCTN Registry within 18 months of trial completion, and we hope to publish the results in an open access peer reviewed journal. The trial was registered retrospectively with ISRCTN on 21st February 2020 (ISRCTN97417474).

Reporting guidelines

This protocol is reported in line with the SPIRIT guidelines. A completed SPIRIT checklist for this protocol is available on the ISRCTN registry (ISRCTN97417474).

Discussion/implications

A recent survey of UK palliative care specialists reported the majority (68%) only screened for delirium when suspected clinically, and few (5%) screened routinely on admission to palliative care units. Only a third of respondents (37%) used assessment tools to screen for delirium, despite international guidance advocating their use. Inadequate delirium training and guidance, as well as the ‘complexity of patient’s conditions’ were perceived as barriers to delirium screening. The consequence of these barriers and the ‘complexity of patient’s conditions’ were perceived as barriers to delirium screening.

The anonymised data will be shared on the ISRCTN Registry within 18 months of trial completion, and we hope to publish the results in an open access peer reviewed journal. The trial was registered retrospectively with ISRCTN on 21st February 2020 (ISRCTN97417474).

Declarations

Ethics approval and consent to participate

Approval was granted by NHS Scotland A Research Ethics Committee (REC reference 19/SS/0091 on 15th October 2019) and Marie Curie Research Governance committees. Participants will receive verbal and written information about the study, and sign a consent form, prior to assessments being conducted. If a participant lacks capacity to decide, signed consent will be sought from their legal proxy, as permitted by the Adults with Incapacity (Scotland) Act 2000.

Trial sponsor

The Academic and Clinical Central Office for Research and Development (ACCORD), is a partnership between the University of Edinburgh and NHS Lothian Health Board. Address: Queen’s Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ. Sponsor number: AC19073.

Data availability

No data are associated with this article.

References


