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1 **Title: Delirium detection in older acute medical inpatients: a**
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3 **multicentre prospective comparative diagnostic test accuracy**
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6 **study of the 4AT and the Confusion Assessment Method**
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1 **Abstract**

2 **Background**

3 Delirium affects >15% of hospitalised patients but is grossly underdetected, contributing to
4 poor care. The 4 'A's Test (4AT; www.the4AT.com) is a short delirium assessment tool
5 designed for routine use without special training. The primary objective was to assess the
6 accuracy of the 4AT for delirium detection. The secondary objective was to compare the
7 4AT with another commonly-used delirium assessment tool, the Confusion Assessment
8 Method (CAM).

9 **Methods**

10 This was a prospective diagnostic test accuracy study set in Emergency Departments or
11 acute medical wards involving acute medical patients aged ≥ 70 . All those without acutely
12 life-threatening illness or coma were eligible. Patients underwent (1) reference standard
13 delirium assessment based on DSM-IV criteria and (2) were randomised to either the index
14 test (4AT, scores 0-12; prespecified score of >3 considered positive) or the comparator
15 (CAM; scored positive or negative), in a random order, using computer-generated pseudo-
16 random numbers, stratified by study site, with block allocation. Reference standard and 4AT
17 or CAM assessments were performed by pairs of independent raters blinded to the results
18 of the other assessment.

19 **Results**

20 843 individuals were randomised: 21 withdrew, 3 lost contact, 32 indeterminate diagnosis,
21 2 missing outcome; 785 were included in the analysis. Mean age was 81.4 (SD 6.4) years.

1 12.1% (95/785) had delirium by reference standard assessment, 14.3% (56/392) by 4AT,
2 and 4.7% (18/384) by CAM. The 4AT had an area under the receiver operating characteristic
3 curve of 0.90 (95% CI 0.84-0.96). The 4AT had a sensitivity of 76% (95% CI 61-87%) and
4 a specificity of 94% (95% CI 92-97%). The CAM had a sensitivity of 40% (95% CI 26-
5 57%) and a specificity of 100% (95% CI 98-100%).

6 **Conclusions**

7 The 4AT is a short, pragmatic tool which can help improving detection rates of delirium in
8 routine clinical care.

9 **Registration**

10 International standard randomised controlled trial number (ISRCTN) 53388093.

11 **Funding source**

12 National Institute of Health Research Health Technology Assessment Programme (NIHR
13 HTA) grant number 11/143/01. CJW was also supported in this work by NHS Lothian via
14 Edinburgh Clinical Trials Unit. The views expressed are those of the authors and not
15 necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

17 **Keywords**

18 Delirium; diagnostic test accuracy; 4AT; Confusion Assessment Method (CAM);
19 sensitivity; specificity; hospital

1 **Background**

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3
4 2 Delirium is a severe neuropsychiatric syndrome, usually triggered by underlying medical
5
6 3 illness, surgery or drugs, which affects at least 15% of hospital inpatients [1-4]. It is more
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8 4 common in older people [5] and people with dementia [6]. Delirium comprises acute onset
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10 5 of disturbances in arousal, attention and other domains of cognition, hallucinations and
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12 6 delusions [7, 8]. Delirium is important because as well as being highly prevalent in
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14 7 hospitalised patients, it strongly predicts poor outcomes such as falls, other medical
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16 8 complications, new institutionalisation and mortality [1, 6, 9-13]. It is also associated with
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18 9 patient and carer distress [14-16]. At least two-thirds of cases are not identified in
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20 10 Emergency Department and general medical settings [17-21]. The reasons for this include
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22 11 time constraints, and lack of education and training [22-24]. Because formal psychiatric
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24 12 assessment for delirium diagnosis takes considerable time, guidelines and pathways
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26 13 advocate use of brief assessment tools for delirium detection. Two assessment tools
27
28 14 extensively used in clinical practice are the 4 'A's Test (4AT) and the short form of the
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30 15 Confusion Assessment Method (CAM).

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34 16 The 4AT [25, 26] comprises four items: (A) Alertness, (B) Abbreviated Mental Test-4; (C)
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36 17 Attention (Months Backwards test); and (D) Acute change or fluctuating course [25, 27],
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38 18 Figure 1. The 4AT was not derived directly from a single set of diagnostic criteria; rather it
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40 19 has items that inform the core features of standard diagnostic criteria. It has a score range of
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42 20 0-12, with scores of 4 or more (>3) suggesting possible delirium. The structure of the 4AT
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44 21 is designed such that there are different ways of reaching an overall positive score (>3).
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46 22 Items (A) and (D) each give a score of 0 if negative, and 4 if positive. The rationale for items
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48 23 (A) and (D) individually potentially triggering an overall positive 4AT score is that altered
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1 arousal and acute change are both highly specific features of delirium [28-30]. The AMT-4
2 (B) gives a score of 1 for one mistake, and 2 for two or more mistakes or if the patient is
3 untestable. The attention test (C) gives a score of 1 if unable to complete 7 months
4 backwards, and 2 if untestable. Therefore patients who perform poorly or are untestable on
5 both cognitive tests (B+C), score 4 from items (B) + (C), triggering further assessment for
6 delirium. The rationale for the (B) and (C) scoring is that many patients with delirium are
7 unable to undergo cognitive testing because of reduced arousal or other reasons [31, 32],
8 and they would be unscorable or scored as negative on assessments that require cognitive
9 testing, but the 4AT identifies that further assessment is required. The 4AT takes around 2
10 minutes and does not require special training. It is recommended in several pathways and
11 guidelines and is in wide routine clinical use in the UK and internationally. Since publication
12 on a dedicated website [26] in 2011, the 4AT has to date been evaluated in eight validation
13 studies [25, 33-39] involving a total of 2577 patients, 479 with delirium. These studies have
14 used varying designs, reference standards, clinical populations, and inclusion criteria.
15 Sensitivities are reported as 83-100% and specificities ranging from 70-99%.

17 **Figure 1. The 4 'A's Test (4AT)**

18
19 The CAM (short form) [28] comprises brief cognitive testing and interview followed by a
20 four-item algorithm in which four DSM-III-R criteria for delirium are rated as being present
21 or absent: (A) acute onset and fluctuating course, (B) inattention, (C) disorganised thinking
22 and (D) level of consciousness. To score positive on the CAM, both (A) and (B) must be
23 positive, plus either or both of (C) and (D). The CAM requires specific training in rating

1 each of the features. The cognitive testing which is carried out before completing the
2 algorithm is not specified in the manual [40]. With the pre-algorithm interview and cognitive
3 testing it takes 5-10 minutes to complete [40]. The CAM is included in multiple international
4 guidelines and pathways, including the UK NICE Guidelines on Delirium published in 2010
5 [41]. According to published systematic reviews [42-46] and a literature review carried out
6 on 19 Feb 2019, the CAM has been evaluated in 22 validation studies since publication in
7 1990 [31, 47-67], with a total of 2437 participants (620 with delirium). As with the 4AT
8 validation studies, these studies vary in design, population, etc. The reported range of
9 sensitivities for delirium detection is 13-100%, and the range of specificities 84-100%.

10 The primary objective of the present study was to conduct an evaluation of the diagnostic
11 accuracy of the 4AT for delirium against a reference standard based on DSM-IV in patients
12 aged 70 years and over recently admitted to hospital recruited prospectively. The secondary
13 objective was to compare the diagnostic test accuracy of the 4AT and CAM. The rationale
14 for performing the comparison is that the 4AT and CAM are both widely used and
15 recommended, yet the 4AT and CAM differ in their scoring systems, and the 4AT offers
16 potential advantages include a shorter testing duration and no need for specific training, and
17 a process for handling untestable patients. Given these differences, it is of interest to
18 practitioners and researchers to know if performance of the 4AT is at least equivalent to the
19 CAM. Additionally, both the 4AT and the CAM have been evaluated in multiple validation
20 studies, but there are no published studies comparing performance of these tools under the
21 same study conditions.

1 **Methods**

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4 2 We followed the Standards for Reporting Diagnostic Accuracy (STARD) 2015 guidelines
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7 3 [68] for reporting diagnostic accuracy studies. The study was registered: International
8
9 4 standard randomised controlled trial number (ISRCTN) 53388093. UK Clinical Research
10
11 5 Network ID: 19502, and the protocol published before database lock and statistical analysis
12
13 6 [69]. The objectives described in the protocol not reported here (e.g. 12 week outcomes)
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15 7 will be disseminated separately.
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21 **Study design: overview**

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24 9 The study protocol has been published [69]. In summary, patients aged 70 or over in
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26 10 Emergency Departments or acute general medical wards were prospectively recruited in
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28 11 three UK sites (Edinburgh, Bradford, and Sheffield). Each patient underwent (a) a reference
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30 12 standard delirium assessment lasting up to 20 minutes, and (b) either the 4AT or the CAM.
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32 13 Participants were randomised to the 4AT or the CAM and also to the ordering of the
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34 14 reference standard and the 4AT or CAM assessment. The study flowchart is shown in Figure
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46 **Figure 2. Diagnostic accuracy study: overview flowchart**

1 **Participants**

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4 2 Potentially eligible participants were those without acutely life-threatening illness or coma,
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6 3 in the Emergency Department or acute general medical wards. Initially the recruitment
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8 4 windows were four hours for the Emergency Department and 24 hours for the acute general
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11 5 medical wards. Four months after study commencement (from 19 February 2016) these
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13 6 were extended to 12 hours and 96 hours respectively to facilitate recruitment, particularly
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15 7 with respect to seeking proxy consent. The potential impact of this was explored in planned
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18 8 subgroup analyses.

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22 9 Patients were recruited by researchers between 0800 and 2200, Monday to Friday, from
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24 10 eligible patients identified by the clinical team. Patients were initially approached
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27 11 alphabetically, then in approximately the last third of the recruitment period, through liaison
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29 12 with clinical staff, prioritising those at higher risk of delirium on clinical grounds (e.g. older
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31 13 age, likely to be admitted, higher degree of ongoing acute and chronic illnesses) to obtain a
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34 14 more representative sample of participants [69] because interim analysis found a lower than
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36 15 expected rate of recruitment of patients who lacked capacity and thus required proxy
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39 16 consent. These changes to the recruitment processes were approved by the Trial Steering
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41 17 Committee. Informed consent was sought by trained researchers. Where the potential
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44 18 participant lacked capacity to consent, recruitment proceeded under the provisions of the
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46 19 Mental Capacity Act, 2005 in England or Adults with Incapacity (Scotland) Act, 2000, using
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49 20 an appropriate personal or nominated consultee, guardian, welfare attorney or nearest
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51 21 relative [69].

1 **Test methods**

2 2 Researchers were nurses or trained graduate clinical research associates who underwent a
3 3 systematic and detailed training process involving teaching on delirium and dementia
4 4 assessment [69]. Additionally, training on the CAM was provided according to the guidance
5 5 given in the CAM instruction manual [40]. Specific training on the 4AT was not provided
6 6 as the tool was designed such that this is not required. The study team had regular
7 7 teleconferences to discuss the conduct of the study.

8 8 The reference standard assessment was based on DSM-IV. These diagnostic criteria were
9 9 used rather than DSM-5 because the study, ethics applications and training procedures were
10 10 initiated at a similar time to publication of DSM-5 and it was not yet in use by the study
11 11 team; because DSM-IV had been used in large numbers of delirium studies thus providing
12 12 more direct comparability with the existing literature; and because of concern that there was
13 13 insufficient time to develop and test valid methods for reference standard assessment using
14 14 DSM-5. The reference standard drew from several sources of information including all
15 15 items from the Delirium Rating Scale-Revised-98 (DRS-R98)[70] and using the instructions
16 16 from the manual, which include raters seeking informant history and inspection of clinical
17 17 records, and a set of neuropsychological tests designed to detect core features of delirium
18 18 [71, 72] comprising Observational Scale for Level of Arousal [29, 73], the Richmond
19 19 Agitation-Sedation Scale [74], Digit Span [75], the Vigilance A test [76], the DelApp
20 20 objective test of attention [77-79], and standard object naming and orientation questions.
21 21 These assessments were used together to inform a binary diagnosis of delirium based on
22 22 DSM-IV criteria. The initial diagnosis was recorded by the researcher performing the
23 23 assessment for the purposes of providing immediate information to the clinical team. These
24 24 initial results of the reference standard assessment were provided by this researcher to the

1 clinical teams after the study 4AT or CAM were completed, through both an entry in the
2 clinical notes, and a verbal discussion. The final and definitive ascertainment for the study
3 was performed later, via expert consensus from a panel comprising ZT (a psychologist),
4 SDS (a geriatrician) and AMJM (a geriatrician), each with many years of experience of
5 delirium assessment (>1000 episodes individually). This final ascertainment was based on
6 the information generated by the reference standard assessment in relation to the DSM-IV
7 criteria, blinded to knowledge of whether the participant had undergone the 4AT or CAM,
8 or the results of these tests. Where there was disagreement, the panel discussed each case
9 using the available information and reached consensus. Where the reference standard
10 assessment results did not provide enough information to provide a definite diagnosis of
11 delirium, the ascertainment was judged to be indeterminate.

12 The 4AT was scored according to the guidance notes on the 4AT form [26], using a
13 combination of sources of available information including casenotes, informants, and
14 bedside assessment. As per the initial design of the 4AT, scores of >3 were used to indicate
15 possible delirium. If patients were unable to undergo cognitive testing because of reduced
16 arousal, the cognitive items 2 and 3 were scored as 'untestable' and each given a score of 2
17 as per the 4AT guidance notes.

18 The CAM algorithm was scored following an interview and set of cognitive tests, and other
19 sources of available information including casenotes and informants, as recommended in
20 the CAM instruction manual [40]. The interview comprised general questions about the
21 patient's hospital stay followed by a set of cognitive tests comprising: days of the week
22 backwards, counting from 20 down to 1, orientation (current day, identifying if it is day or
23 night, current year, last meal, how long in hospital, city, name of the hospital, floor of the
24 hospital), memory (3 word recall immediately, up to 3 trials until all 3 words recalled or 3

1 trials repeated; then recall at 5 minutes), and clock drawing. The CAM algorithm was scored
2 as per the instruction manual. Where an item could not be assessed, for example, if the
3 patient was unable to speak or write and thus could not undergo assessment for disorganised
4 thinking (see instruction manual), the item was scored as negative.

5 The presence of dementia was sought through either a formal diagnosis of dementia in the
6 clinical records and/or, when possible, the Informant Questionnaire on Cognitive Decline
7 in the Elderly (IQCODE) using a cut-off score of ≥ 3.44 [80].

8 **Ordering of reference standard delirium assessment, 4AT and CAM**

9 After the consent process was complete, participants were randomised in a 1:1 ratio to (a)
10 reference standard first then either 4AT or CAM or (b) either 4AT or CAM first then
11 reference standard via a secure online system using computer-generated pseudo-random
12 numbers, stratified by study site, with block allocation. The reference standard assessment
13 was performed by the researcher who conducted the capacity assessment and consenting
14 process. A different researcher from the one performing the reference standard assessment
15 performed either the 4AT or the CAM. Researchers performed the 4AT or the CAM
16 according to the randomisation, with no individual researcher responsible for performing
17 either the 4AT or the CAM; that is, each researcher performed approximately equal numbers
18 of the 4AT and the CAM. The two assessments took place strictly within a maximum of two
19 hours of each other, with a target interval of 15 minutes. Researchers were blinded to each
20 other's assessments, that is, reference standard results were not available to performers of
21 the index and comparator tests, and vice versa. The design of either 4AT or CAM rather
22 than both 4AT and CAM being performed by each participant was chosen to avoid burden
23 on participants, and because the CAM testing process is longer than the 4AT and

1 information from the CAM process could influence scoring of the 4AT; some influence of
2 4AT item scores on the CAM could also be possible.

3 **Statistical Analysis**

4 All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, United
5 States).

6 **Primary objective**

7 We calculated positive and negative predictive values, sensitivity and specificity for 4AT
8 versus the reference standard. We reported the area under the receiver operating
9 characteristic (ROC) curve and its 95% confidence interval (CI) for the 4AT.

10 **Secondary objective**

11 Comparison of 4AT and CAM: we calculated positive predictive values (PPV) and negative
12 predictive values (NPV), sensitivity and specificity (with exact binomial 95% CI) for CAM
13 and 4AT, and estimated the difference (4AT minus CAM) for each, assessing statistical
14 significance of differences using Fisher's exact test. The area under the ROC curve could
15 not be calculated for the CAM as the outcome is binary. The overall performance of 4AT
16 and CAM were each summarised using Youden's Index (sensitivity minus false positive
17 rate) and the diagnostic odds ratio of sensitivity to specificity.

18 **Subgroup analyses**

19 Predefined subgroup analyses assessed the impact of (a) time from presentation to
20 recruitment (analysing those tested before or after 4h (ED) or 24h (medical admissions)) for

1 4AT, and (b) time between index test and reference standard (analysing those tested within
2 30 minutes compared to those tested later) for both 4AT and CAM.

3 **Sensitivity analyses**

4 We performed predefined sensitivity analyses where the reference standard was
5 indeterminate by defining delirium as present, and then absent. We also performed a post
6 hoc sensitivity analysis by using the initial delirium classification recorded by the researcher
7 at the time of the original bedside assessment (which was performed to inform clinical staff
8 at that time). A further post-hoc sensitivity analysis assumed that any patient with a missing
9 result for the index test (4AT or CAM) had delirium.

10 **Missing data**

11 If data were missing for the reference standard assessment, CAM or 4AT, or if the reference
12 standard assessment did not yield a clear diagnosis, data from these individuals were
13 removed from statistical analysis.

14 **Sample size**

15 We planned to randomise 900 patients, 450 to assessment by 4AT and 450 to CAM. For
16 each of 4AT and CAM the width of the two-sided 95% confidence interval for specificity
17 would be up to ± 0.050 ; and for sensitivity, up to ± 0.120 . The secondary objective comparing
18 4AT and CAM would have 83% power to detect a difference in specificity of 0.10 and 80%

1 power to detect a difference in sensitivity of 0.22, for a 5% two-sided significance level and
2 analysis by continuity corrected chi-squared test.

5 **Results**

6 Study recruitment commenced on 19 October 2015, and was completed on 30 December
7 2016, with final follow-up data collection and locking of the database on 29 June 2017.
8 4,928 patients were eligible, from whom 843 individuals (17.1%) were recruited across the
9 three sites, and two withdrew before data collection, leaving 841 with data for analysis of
10 whom 19 withdrew, 3 lost contact, 32 were classified as indeterminate from the reference
11 standard data, and 2 had a missing outcome. Therefore, 785 individuals were included in
12 the analyses (Figure 3). Recruitment did not reach the target of 900 through a combination
13 of a lower than expected rate of recruitment and a limit to the available recruitment period.
14 However, the number recruited allowed for adequate power to test the main hypotheses as
15 confirmed by the study statisticians and the Trial Steering Committee.

18 **Figure 3. STARD diagram of flow of participants through the study (total across all
19 three sites)**

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2 Reference standard delirium prevalence was 12.1% (n=95 of 785). Individuals with delirium
3 were older and were more likely to have dementia as documented through the clinical
4 records or through the informant questionnaire (Table 1). Baseline characteristics for those
5 randomised to the 4AT or CAM are shown in Additional Table 1. Reference standard
6 delirium prevalence in those who had a valid 4AT assessment was 12.5% (n=49 of 392),
7 and in those who had a valid CAM assessment was 10.9% (n=42 of 384). Delirium
8 prevalence using the 4AT only as a diagnostic test was 14.3% (n=56 of 392) and for CAM
9 only as a diagnostic test was 4.7% (n=18 of 384).

Table 1. Baseline demographic and clinical characteristics stratified by reference standard delirium status

	Total (N=785)	Delirium Present (N=95)	Delirium Absent (N=690)	P value
Age (Years)				
Mean (SD)	81.4 (6.4)	83.5 (6.9)	81.1 (6.3)	0.0007
Median [Q1-Q3]	81.0 [77.0-86.0]	84.0 [78.0-89.0]	81.0 [77.0-86.0]	
Gender				
Male, n (%)	349 (44.5%)	34 (35.8%)	315 (45.7%)	0.0697
Female, n (%)	436 (55.5%)	61 (64.2%)	375 (54.3%)	
Dementia Diagnosis and/or IQCODE^a ≥ 3.44^a				
Yes, n (%)	111 (14.2%)	43 (45.3%)	68 (9.9%)	<0.0001
No, n (%)	673 (85.5%)	52 (54.7%)	621 (90.1%)	
Missing, * n (%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	
Location of First Assessment				
Emergency Department, n (%)	53 (6.8%)	10 (10.5%)	43 (6.2%)	0.2624
Acute General Medical Ward, n (%)	665 (84.7%)	76 (80.0%)	589 (85.4%)	
Hospital Ward, n (%)	67 (8.5%)	9 (9.5%)	58 (8.4%)	

P-value from chi-squared (categorical variables) or t-test (continuous).

*Missing category not included in chi-squared test.

^aIQCODE is Informant Questionnaire for Cognitive Impairment in the Elderly.

1 **Diagnostic test accuracy of 4AT and CAM**

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4 2 The main diagnostic test accuracy results for the 4AT and CAM are shown in Table 2. At a
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7 3 4AT cut-off score for delirium of >3, the sensitivity was 76% (95% CI 61 to 87%) and the
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9 4 specificity was 94% (95% CI 92 to 97%). The performance at different cut-off scores is
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11 5 shown in Additional Table 2. The area under the ROC curve for the 4AT was 0.90 (95% CI
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13 0.84 to 0.96) (Figure 4). The CAM had a sensitivity of 40% (95% CI 26 to 57%) and a
14 6
15 specificity of 100% (95% CI 98 to 100%).
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27 10 **Figure 4. Receiver Operator Characteristic Curve for 4AT diagnostic accuracy**
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Table 2. Diagnostic test accuracy of the 4AT the CAM for diagnosis of delirium (defined by reference standard assessment)

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Youden's Index
4AT (>3), <i>n</i> (95% CI)	76% (61 to 87%)	94% (92 to 97%)	66% (52 to 78%)	96% (94 to 98%)	0.70
CAM Positive, <i>n</i> (95% CI)	40% (26 to 57%)	100% (98 to 100%)	94% (73 to 100%)	93% (90 to 96%)	0.40
Difference in Proportions	36% (15 to 53%)	-6% (-14 to 2%)	-28% (-53 to -2%)	3% (-4 to 11%)	
<i>P</i> value	0.0012	<0.0001	0.0297	0.0629	

Numbers are estimates (95% CI). Youden's Index is equal to sensitivity+specificity-1, a value of zero indicates no value, and a value of 1 indicates a perfect test. The Difference in Proportions is 4AT-CAM for each of the tabulated measures of diagnostic accuracy, accompanied by the corresponding P-value from the Fisher's exact test comparing proportions. Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

1 **Subgroup analyses**

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4 2 There was no statistically significant difference in the diagnostic test accuracy of the 4AT
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6 3 between those recruited early and those recruited later after initial presentation (Fisher's
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8 4 Exact Test p-values: sensitivity p=0.19, specificity p=0.75, PPV p=0.47, NPV p=0.24).

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11 5 There was no statistically significant difference in performance of either test regardless of
12
13 6 whether or not it was performed within 30 minutes of the reference standard (Fisher's Exact
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15 7 Test p-values: sensitivity p=0.16, specificity p=0.24, PPV p=1.00, NPV p=0.56).

16 8 **Sensitivity analyses**

17 9 **Indeterminate reference standard**

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22 10 Assuming delirium was present for all indeterminate reference standards (N=32) reduced
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24 11 the sensitivity of both the 4AT and CAM: 64% (95% CI 52 to 76%), and 33% (95% CI 21
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26 12 to 47%), respectively (Additional Table 3). Assuming delirium was absent for all
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28 13 indeterminate reference standards did not substantially alter the diagnostic accuracy of the
29
30 14 4AT or CAM (Additional Table 4).

31 15 **Delirium reference standard**

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34 16 Using the researchers' initial reference standard assessment of delirium, the sensitivity of
35
36 17 the 4AT was 83% (95% CI 70 to 93%) and the specificity was 94% (95% CI 91 to 96%).
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38 18 The sensitivity (40%; 95% CI 25 to 56%) and specificity (99%; 95% CI 98 to 100%) of the
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40 19 CAM did not change substantially.

1 **Missing index test**

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4 2 If delirium was scored as present where the index test result was missing, this did not
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6 3 substantially alter the diagnostic test accuracy of the 4AT or CAM (Additional Table 5).
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18 **Discussion**

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22 7 This study found that the 4AT had a sensitivity of 76% and a specificity of 94% for delirium
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24 8 as assessed independently by a reference standard. The area under the ROC curve was high
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27 9 at 0.90. These findings, in a relatively large, STARD-compliant study, provide support
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30 10 additional to the existing literature for the use of the 4AT as a delirium assessment
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32 11 instrument in clinical practice which has acceptable overall diagnostic test accuracy. The
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34 12 study also found that the CAM showed lower sensitivity than the 4AT, at 40%, with higher
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37 13 specificity at 100%. This is the first randomised comparison of two of the most widely used
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39 14 delirium assessment tools in clinical practice, and thus is informative for researchers with
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42 15 respect to their respective performance under the same study conditions.
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45 16 The diagnostic test accuracy of the 4AT was broadly similar to the existing studies [25, 33-
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47 17 39], albeit with lower sensitivity and higher specificity than most prior studies. The
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50 18 difference in the sensitivity results may reflect differences in study population, the reference
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53 19 standard assessment, and recruitment processes. One prior study found higher sensitivity
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55 20 (87%) and lower specificity (70%) and a similar area under the ROC curve of 0.84 in an
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58 21 unselected consecutive clinical sample using a design that did not require consenting
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1 (N=434)[35]. The 4AT involves a degree of subjectivity with respect to the assessment of
2 level of alertness; raters are asked to rate this in a binary fashion, that is, as abnormal or
3 normal. The reference standard assessment involves a more detailed approach to assessment
4 of arousal involving the three different tools: the Observational Scale of Level of Arousal,
5 the Richmond Agitation-Sedation Scale, and the arousal element of the DelApp smartphone
6 test of attention and arousal. It is possible that the simpler binary assessment tended to a
7 lower level of positive score than the more complex and nuanced reference standard
8 assessment process. Additionally, the bedside element of the 4AT (items 1-3) usually takes
9 less than one minute, as compared to around 20 minutes for the reference standard
10 assessment. This give more opportunity in the reference standard assessment for the
11 observation of reduced arousal as well as fluctuation of symptoms. Further planned analyses
12 of the present dataset will explore the relationships of individual test components of the 4AT
13 (and the CAM) to the overall test score and components of the reference standard.

14 In this study the CAM showed very high specificity and modest sensitivity for delirium. The
15 high specificity is aligned with prior studies, the vast majority of which have found
16 specificities of over 90%. The sensitivity of 40% was lower than in the majority of published
17 studies. However, unlike with specificity, the literature shows notable heterogeneity in
18 findings with respect to CAM sensitivity, with several studies also showing lower
19 sensitivities for the CAM [48, 50, 51, 57, 65, 67]. Differences in study populations,
20 eligibility criteria (e.g. exclusion of drowsy patients unable to produce speech), the
21 interview and cognitive testing performed, the training provided (this is variably described
22 in the literature), and the background and experience of the raters may all play a role in the
23 variability of findings [48, 59, 81]. The CAM involves binary, subjective bedside
24 judgements of inattention, disorganised thinking, and level of consciousness; such

1 judgements are more open to variability between raters compared to objective scoring [72,
2 75]. Another possible source of reduced sensitivity in some studies is that the CAM
3 algorithm generates a negative score if disorganised thinking is not ascertained (that is, if
4 ‘rambling, irrelevant or incoherent speech’ [40] is not judged to be present) and if the level
5 of consciousness is judged to be normal, though the patient may have inattention and other
6 cognitive deficits and thus meet DSM-IV or DSM-5 criteria for delirium. Similarly, if
7 inattention is not judged to be present but there is altered level of consciousness the CAM
8 algorithm will generate a negative score.

9 This study had several strengths. Each participant was randomised to perform either the 4AT
10 or CAM under the same study conditions, with the reference standard being performed
11 independently by a different researcher. This is of interest given that the 4AT and the CAM
12 are two of the most commonly-used tools internationally. Researchers were formally trained
13 in use of the CAM and the reference standard assessment. The reference assessment
14 involved gathering information from the DRS–R98, several tests of cognition and also level
15 of arousal. Neufeld and colleagues [82] found substantial variability in delirium reference
16 standard assessments used in diagnostic accuracy studies of delirium assessment tools, with
17 many not using cognitive testing as part of the assessment process. The present study had
18 limited exclusion criteria, allowing patients with a wide spectrum of level of severity to be
19 approached, including patients with severely reduced level of arousal. This is pertinent
20 because reduced level of arousal is common in emergency admissions; in one study of
21 clinically-collected data from 35,585 consecutive, unselected acute medical admissions
22 aged >15, 7.6% of patients had reduced level of arousal above the level of coma, and in
23 older populations the prevalence is are higher [73, 83-85]. Given the close relationship of
24 reduced arousal with delirium [29, 32, 73, 85, 86] it is important that studies of delirium

1 assessment instruments include the full spectrum of patients with reduced arousal
2 (excluding coma). The study was relatively large, and multicentre. The protocol was
3 published in advance of database lock and analysis, and the study reporting adhered to the
4 STARD guidelines.

5 Some limitations of this study should be acknowledged. In this study only 17% of those
6 eligible for recruitment were recruited, mostly due to patients declining to participate or no
7 person available to provide proxy consent. The delirium rate was 12.1% according to the
8 reference standard; prior studies have estimated that the prevalence of delirium in patients
9 aged 70 or above at the early stages of hospital admission likely ranges from 10 to 20% [87].
10 The recruitment process, which required consenting (often from a proxy), may have led to
11 a sample with a moderately lower delirium prevalence than in clinical populations. This is
12 a known limitation of delirium studies requiring consent [88]. Most patients with delirium
13 lack capacity, and in the context of the present study this necessitated proxy consent and an
14 informant to score the acute change items in the 4AT and CAM. In clinical practice, the
15 acute change item might be informed by staff knowledge of the patient, or not scored if no
16 such information exists (though an overall positive score is still possible on the 4AT because
17 of the scoring procedure for items (A), (B), and (C); this differs from the process that was
18 required in the study. With respect to the reference standard, it is possible that objective
19 assessments recorded and interpreted for this did not fully capture the researcher's
20 interaction with the patient and thus the researcher's ascertainment of DSM-IV delirium
21 features. Results from the sensitivity analysis using bedside reference standard diagnosis
22 support this possibility, showing higher rates of both sensitivity (83%) and specificity (94%)
23 if the researcher's initial assessment was used. We aimed to ascertain dementia status but it
24 is possible that some patients had dementia but this was undiagnosed and the IQCODE was

1 unavailable. The number of patients with known dementia was too low to allow analysis of
2 performance of the 4AT or CAM in patients with and without dementia. Finally, it is
3 possible that researcher bias may have influenced the conduct or scoring of the different
4 index assessments (4AT or CAM) because the 4AT was designed in one of the sites of the
5 study and involved AMJM. However none of the researchers collecting data was involved
6 in development of the 4AT, the CAM was performed by researchers trained in its use as
7 advised in the CAM instruction manual, and the reference standard was administered by
8 researchers blind to the identity or results of the index tests.

9 Future studies could seek to compare performance of the 4AT with other short delirium
10 assessment tests, such as the Single Question in Delirium (SQiD)[61], the Delirium Triage
11 Screen [89], the brief CAM (bCAM)[89, 90], the 3D-CAM [91] and the Simple Query for
12 Easy Evaluation of Consciousness (SQeeC)[65]. Studies could also evaluate the value of
13 the individual items of the 4AT. This is an important issue because though ideally informant
14 history is used to make a diagnosis of delirium, in a substantial proportion of patients such
15 history is not available at the point of initial assessment or even during the inpatient stay
16 [35, 38]. Additionally, the extent of real-world use in large clinical datasets including rates
17 of positive scores should be evaluated. For example the 4AT is mandated to assess for post-
18 operative delirium in all acute hip fracture patients in the National Health Service in
19 England, Wales, and Northern Ireland; in 2017 86% of 63,471 patients were assessed with
20 the 4AT, with 25% showing a positive score [92]. This is possibly an underestimate of post-
21 operative delirium rates, but suggests that the 4AT is embedded in routine practice and likely
22 detecting the majority of delirium. Further reporting of use of the 4AT and other tools in
23 other large clinical datasets will be informative in determining feasibility outside of research
24 studies.

1 **Conclusions**

2 The 4AT showed moderate sensitivity, high specificity, and good overall diagnostic
3 performance. In the present study the 4AT showed higher sensitivity than the CAM, and
4 slightly lower specificity under the same study conditions. The CAM has been evaluated by
5 multiple validation studies and while many of these studies show high sensitivity, many also
6 show that sensitivity tends to be lower where raters are not fully trained in the CAM, or who
7 lack specialist training in psychiatric assessment. Taken as a whole, the 4AT validation
8 studies suggest that it has comparable performance to the CAM when the CAM is being
9 performed by trained raters. In terms of its brevity, lack of need for training, and comparable
10 performance the 4AT can therefore reasonably be used as an assessment tool for delirium,
11 particularly in clinical settings in which there is limited time, and in which staff involved in
12 delirium detection cannot undergo the substantial special training required for use of the
13 CAM. Additionally, the 4AT can be scored if no informant history is available at the time
14 of assessment, and if arousal is impaired such that cognitive testing is not possible, which
15 occurs in a substantial proportion of delirium assessments [35, 38, 65]. Given that acutely
16 altered arousal is a highly specific indicator of delirium [29, 30, 72, 73, 85, 93-95] and that
17 it often indicates a poor prognosis [83], a rapid provisional diagnosis of delirium with
18 appropriate action in the absence of an external informant history is reasonable. The 4AT is
19 designed to be able to yield a positive score in patients too unwell to undergo interview or
20 cognitive testing [31, 32]; this facilitates implementation and higher completion rates in
21 clinical practice. It is important to note, however, that as with all short detection tools, formal
22 diagnosis of delirium in clinical practice requires assessment by a suitably-qualified member
23 of staff.

1 **Figure legends**

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4 2 **Figure 1 legend: [no legend]**

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8 3 **Figure 2 legend:** ED = Emergency Department; MOE = Medicine of the Elderly; 4AT =
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10 4 4As Tests; CAM = Confusion Assessment Method

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14 5 **Figure 3 legend: [no legend]**

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18 6 **Figure 4 legend:** 4AT scores range from 0-12. The cut-point of >3 is used in the scoring
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20 7 scheme to denote likely delirium. The 4AT scores are considered against the reference
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22 8 standard delirium assessment.

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26 9 **Additional Table 1: Baseline Characteristics by Index Test (4AT or CAM).** Legend:

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29 10 Numbers are n (%) or mean (SD).

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32 11 **Additional Table 2: Performance of various cut points of 4AT for diagnosis of**

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35 12 **delirium.** Legend: Numbers are estimates (95% CI). Abbreviations: CI, confidence interval;

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37 13 PPV, positive predictive value; NPV, negative predictive value. Youden's Index is equal to

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39 14 sensitivity+specificity-1, a value of zero indicates no value, and a value of 1 indicates a

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42 15 perfect test.

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45 16 **Additional Table 3: Sensitivity analysis of diagnostic test accuracy of 4AT versus CAM**

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47 17 **for diagnosis of delirium assuming all indeterminates are delirium present.** Legend:

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49 18 Numbers are estimate (95% CI). Difference in proportions is for 4AT-CAM. Abbreviations:

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51 19 CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value;

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53 20 OR, odds ratio. Youden's Index is equal to sensitivity+specificity-1, a value of zero indicates

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56 21 no value, and a value of 1 indicates a perfect test.

1 **Additional Table 4: Sensitivity analysis of diagnostic test accuracy of 4AT versus CAM**
2 **for diagnosis of delirium assuming all indeterminates are delirium absent.** Legend:

3 Numbers are estimate (95% CI). Difference in proportions is for 4AT-CAM. Abbreviations:
4 CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value;
5 OR, odds ratio. Youden's Index is equal to sensitivity+specificity-1, a value of zero indicates
6 no value, and a value of 1 indicates a perfect test.

7 **Additional Table 5: Diagnostic test accuracy of 4AT versus CAM for diagnosis of**
8 **delirium, assuming test scored delirium present for those with a missing 4AT or CAM**
9 **score.** Legend: Numbers are estimate (95% CI). Difference in proportions is for 4AT-CAM.

10 Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative
11 predictive value; OR, odds ratio. Youden's Index is equal to sensitivity+specificity-1, a
12 value of zero indicates no value, and a value of 1 indicates a perfect test.

13
14 **List of abbreviations**

- 15 3D-CAM: 3-Minute Diagnostic Assessment for Delirium using the Confusion Assessment
16 Method
17 4AT: 4 'A's Test
18 bCAM: Brief Confusion Assessment Method
19 CAM: Confusion Assessment Method
20 CI: confidence interval

- 1 DSM-III-R: Diagnostic and Statistical Manual, 3rd edition, revised
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- 4 2 DSM-IV: Diagnostic and Statistical Manual, 4th edition
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- 7 3 DSM-5: Diagnostic and Statistical Manual, 5th edition
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- 11 4 ED: Emergency Department
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- 15 5 IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly
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- 18 6 ISRCTN: International standard randomised controlled trial number
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- 22 7 NPV: negative predictive value
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- 26 8 NIHR HTA: National Institute of Health Research Health Technology Assessment
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- 28 9 Programme
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- 32 10 NHS: National Health Service
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- 36 11 PPV: positive predictive value
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- 39 12 REC: research ethics committee
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- 42
- 43 13 ROC: receiver operating characteristic
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- 45
- 46
- 47 14 SQiD: Single Question in Delirium
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- 50 15 SqueC: Simple Query for Easy Evaluation of Consciousness
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- 54 16 STARD: Standards for Reporting Diagnostic Accuracy
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Declarations

Ethics approval and consent to participate

This study was granted ethical approval prior to data collection in Scotland (Scotland A NHS Research Ethics Committee REC 15/SS/0071) and England (Yorkshire and The Humber – Bradford Leeds NHS Research Ethics Committee REC 15/YH/0317).

Consent for publication

Not applicable

Availability of data and materials

Analyses of the data in this study are still ongoing. We shall make fully anonymised data available on the website <https://datashare.is.ed.ac.uk/> in an estimated one year from the publication of this manuscript.

Competing interests

AMJM led the design of the 4AT in 2011 (with others, see www.the4AT.com); note that 4AT is free to download and use. SDS and AA provided comments on its development. SG is chair of the NIHR HTA Clinical Evaluation and Trials Board and member of the NIHR HTA Funding Board Policy Group. The other authors declare no competing interests.

1 design and staff training and supervision. JacqS was a trial statistician and made a substantial
2 contribution to the development of the statistical analysis plan and undertook the statistical
3 analyses. CW was a trial statistician, and co-designed the protocol, led the design of the
4 statistical analysis plan, and oversaw the statistical analyses. AMJM conceived and planned
5 the study and acted as study lead, making substantial contributions to design of the reference
6 standard assessment, statistical analysis and training of research staff.

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10

Figure 1. The 4 'A's Test (4AT)



(label)

Patient name:

Date of birth:

Patient number:

**Assessment test
for delirium &
cognitive impairment**

Date:

Time:

Tester:

CIRCLE

[1] ALERTNESS

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

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

[2] AMT4

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

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

[3] ATTENTION

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

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

[4] ACUTE CHANGE OR FLUCTUATING COURSE

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

No	0
Yes	4

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

4AT SCORE

GUIDANCE NOTES

Version 1.2. Information and download: www.the4AT.com

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

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

Figure 2. Study design overview flowchart

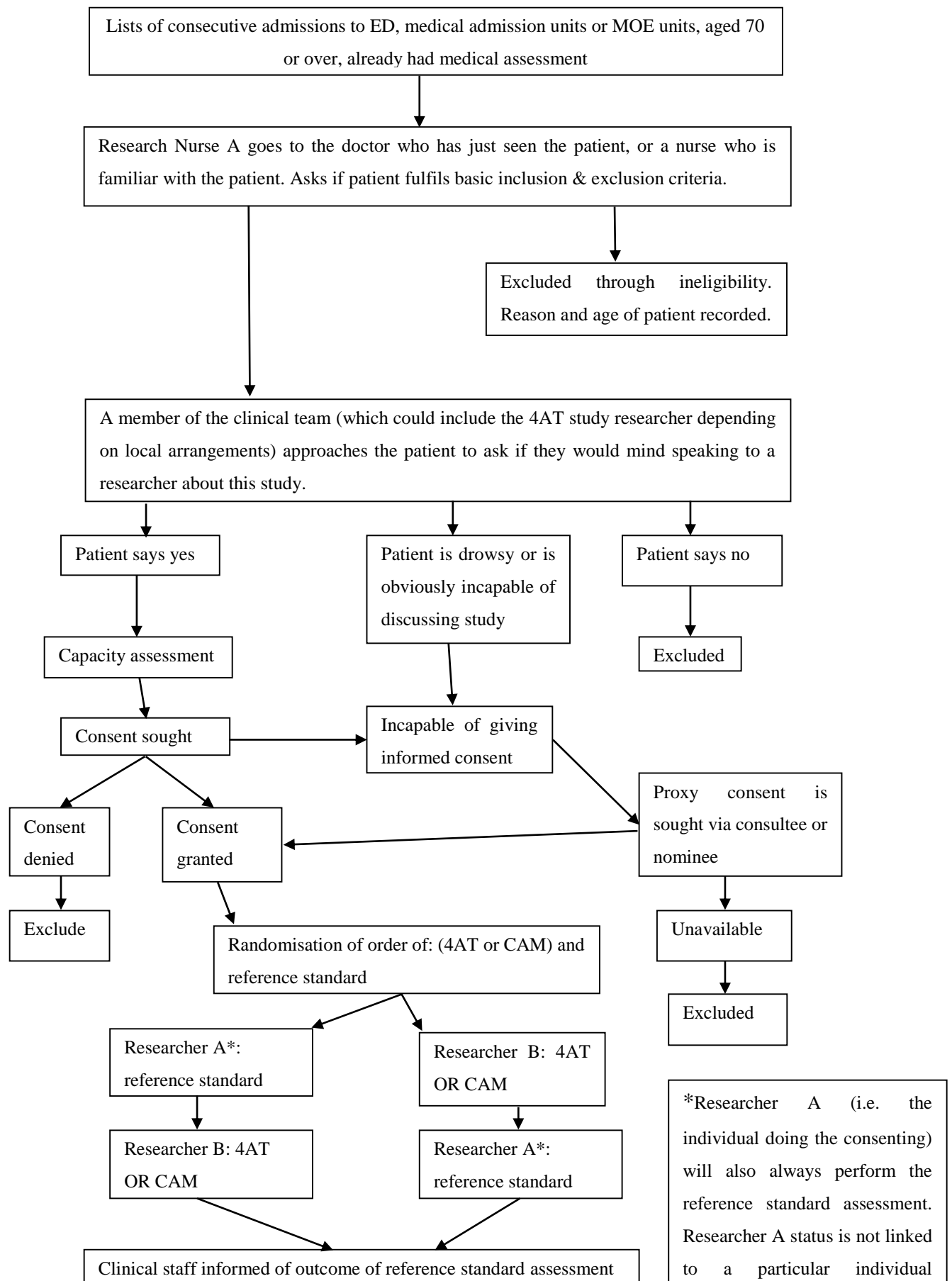


Figure 3.

STARD diagram of flow of participants through the study (total across all three sites)

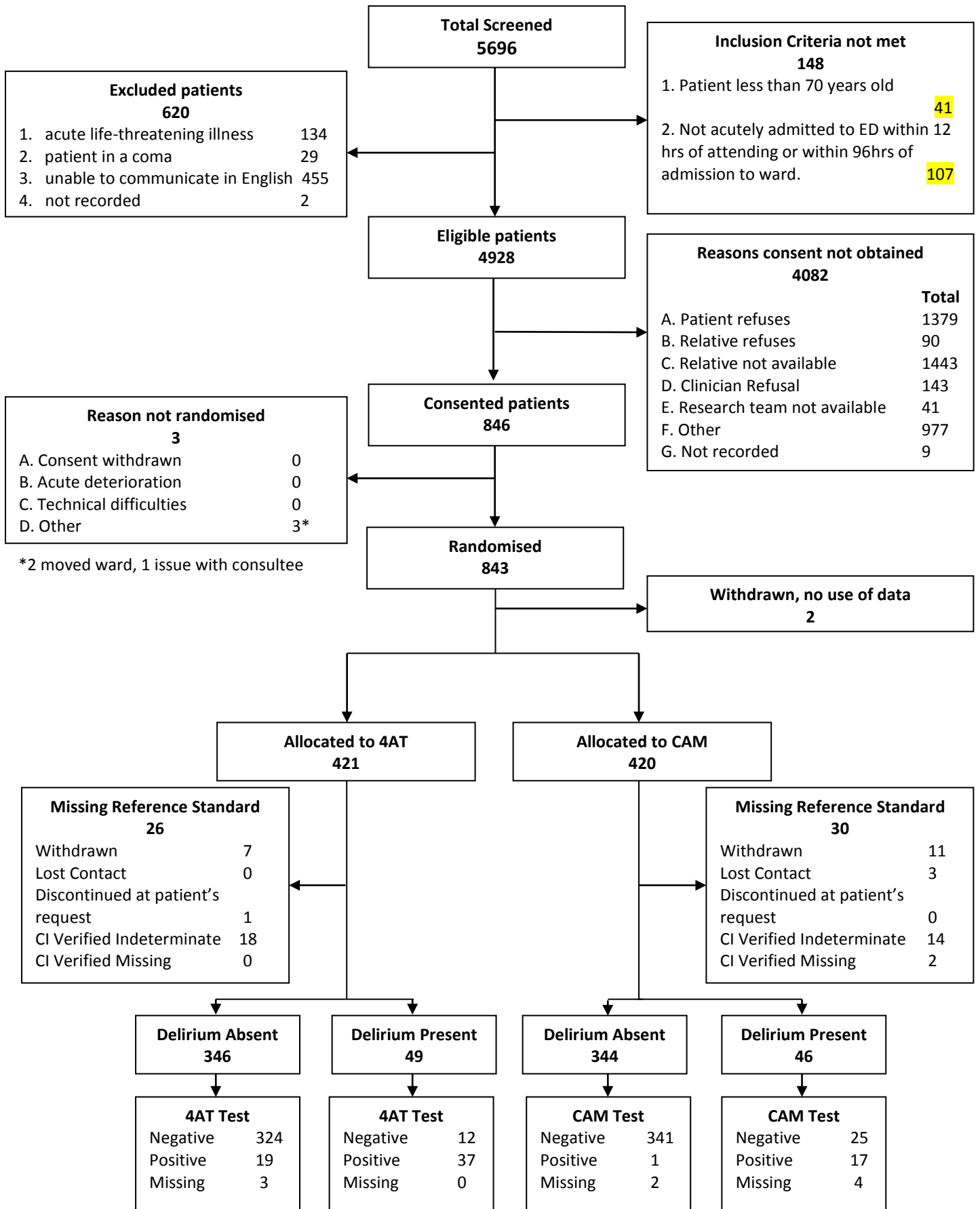
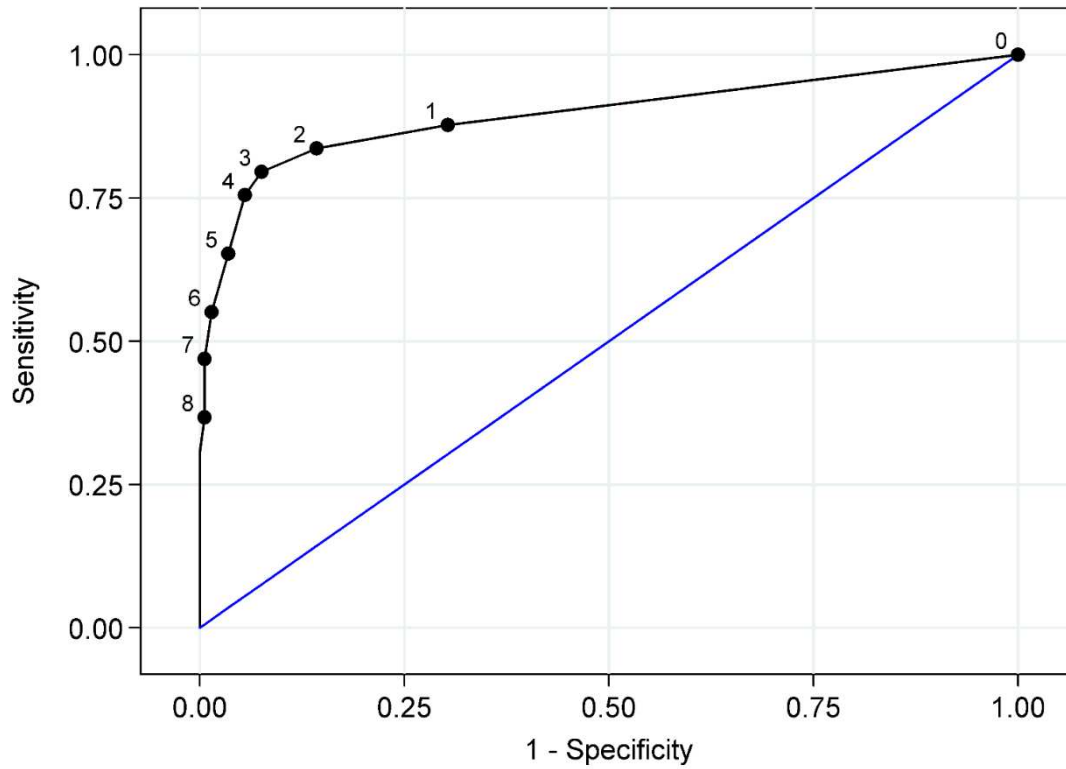


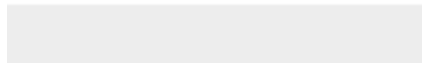
Figure 4. Receiver Operator Characteristic Curve for 4AT diagnostic accuracy

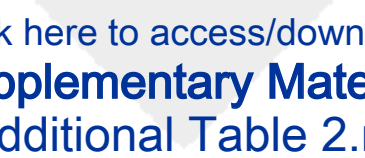


4AT scores range from 0-12. The cut-point of >3 is used in the scoring scheme to denote likely delirium. The 4AT scores are considered against the reference standard delirium assessment.

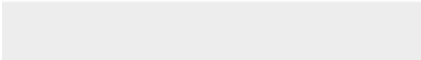



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