CLEMENTI & ASSOCIATES, LTD.
Medical and Regulatory Consulting

K161328

919 Conestoga Road, Building 3, Suite 312
Rosemont, PA 19010

T (610) 527-2600
www.regulatoryaffairs.com

May 10, 2016

Traditional 510(k) Submission

Original Submission

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

RE: Original 510(k) – Cantab Mobile

Dear Sir or Madam:

Cambridge Cognition submits this notification of intent to market Cantab Mobile as described within this Traditional 510(k) submission and includes the required elements identified in 21 CFR 807 Subpart E. Cantab Mobile is a software application intended to be used to assess memory in patients aged 50 to 90 years. Along with the memory test, there are optional mood and functional assessments which can help detect symptoms of depression (Geriatric Depression Screening Questionnaire [GDS]), and problems with performing regular activities of daily living (Activities of Daily Life Questionnaire [ADL]).

Cantab Mobile is not a diagnostic test. A diagnosis can only be made by a qualified physician using consensus diagnostic criteria. The option to test or not to test is a decision that rests with the medical professional.

The content in this 510(k) submission supports the claim that Cantab Mobile is substantially equivalent to the previously approved predicate device, DANA (manufactured by AnthroTronix; K141865). Cantab Mobile and DANA are both categorized as Attention Task Performance Recorders and both are used by healthcare professionals to measure aspects of patients' cognition. In addition, Cantab Mobile and DANA are similar in terms of technological characteristics as both electronically record objective performance measurements when the patient responds to stimuli presented on the screen by touching the screen. Differences in the design and performance of Cantab Mobile and DANA do not affect either the safety or effectiveness of Cantab Mobile for its intended use.

The documents included in this submission (both paper and electronic formats) have been formatted in accordance with the *Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)* and listed on the attached page entitled "Contents of Submission". The eCopy submission is an exact duplicate of the paper copy except for the electronic-only content specified in the Contents of Submission footnotes. For ease of review, these format-specific statements are consolidated here and present in both the eCopy and paper copy.

Clementi and Associates, Ltd. will be responsible for submissions to, and authorized to receive correspondence from the FDA. Clementi and Associates, Ltd. will act as the sole authorized US Agent and all Agency communication should be maintained through Clementi.

If you have any questions, please do not hesitate to contact me at the telephone or email address listed directly below:

Contact person for the 510(k):
William A. Clementi, PharmD, FCP or Nancy D. Clementi, MD
Phone: (610) 527-2600
Secure Email: bill.clementi@clempharma.net or nancy.clementi@clempharma.net

Sincerely,

Nancy Clementi

Nancy D. Clementi, MD
Chief Medical Officer
US Agent for Cambridge Cognition

Encl: FDA Form 3514, Contents of Submission

Form Approved: OMB No. 0910-0511 Expiration Date: April 30, 2016. See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION **MEDICAL DEVICE USER FEE COVER SHEET**	PAYMENT IDENTIFICATION NUMBER: (b)(4) Write the Payment Identification number on your check.
A completed cover sheet must accompany each original application or supplement subject to fees. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment and mailing instructions can be found at: http://www.fda.gov/oc/mdufma/coversheet.html	
1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code) CAMBRIDGE COGNITION LTD Tunbridge Court Tunbridge Lane Tunbridge Court Bottisham Cambridgeshire CB25 9TU GB 1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)	2. CONTACT NAME Nancy Clementi 2.1 E-MAIL ADDRESS nancy.clementi@clempharma.net 2.2 TELEPHONE NUMBER (include Area code) 610-5272600 2.3 FACSIMILE (FAX) NUMBER (Include Area code)
3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm345263.htm Select an application type: [X] Premarket notification(510(k)); except for third party [ ] 513(g) Request for Information [ ] Biologics License Application (BLA) [ ] Premarket Approval Application (PMA) [ ] Modular PMA [ ] Product Development Protocol (PDP) [ ] Premarket Report (PMR) [ ] 30-Day Notice	3.1 Select a center [X] CDRH [ ] CBER 3.2 Select one of the types below [X] Original Application Supplement Types: [ ] Efficacy (BLA) [ ] Panel Track (PMA, PMR, PDP) [ ] Real-Time (PMA, PMR, PDP) [ ] 180-day (PMA, PMR, PDP)
4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status)	

[ ] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA [X] NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number:

5. FDA WILL NOT ACCEPT YOUR SUBMISSION IF YOUR COMPANY HAS NOT PAID AN ESTABLISHMENT REGISTRATION FEE THAT IS DUE TO FDA. HAS YOUR COMPANY PAID ALL ESTABLISHMENT REGISTRATION FEES THAT ARE DUE TO FDA?

[X] YES (All of our establishments have registered and paid the fee, or this is our first device, and we will register and pay the fee within 30 days of FDA's approval/clearance of this device.)

[ ] NO (If "NO," FDA will not accept your submission until you have paid all fees due to FDA. This submission will not be processed; see http://www.fda.gov/cdrh/mdufma for additional information)

6. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.

[ ] This application is the first PMA submitted by a qualified small business, including any affiliates

[ ] The sole purpose of the application is to support conditions of use for a pediatric population

[ ] This biologics application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only

[ ] The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

7. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).

[ ] YES [X] NO

PAPERWORK REDUCTION ACT STATEMENT

Public reporting burden for this collection of information is estimated to average 18 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to the address below.

Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002 [Please do NOT return this form to the above address, except as it pertains to comments on the burden estimate.]

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION

(b)(4) 28-Apr-2016

Form FDA 3601 (05/13)

"Close Window" Print Cover sheet

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May 10, 2016

Traditional 510(k) Submission

Original Submission

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Center for Devices and Radiological Health
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10903 New Hampshire Avenue
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RE: Original 510(k) – Cantab Mobile

Dear Sir or Madam:

Cambridge Cognition submits this notification of intent to market Cantab Mobile as described within this Traditional 510(k) submission and includes the required elements identified in 21 CFR 807 Subpart E. Cantab Mobile is a software application intended to be used to assess memory in patients aged 50 to 90 years. Along with the memory test, there are optional mood and functional assessments which can help detect symptoms of depression (Geriatric Depression Screening Questionnaire [GDS]), and problems with performing regular activities of daily living (Activities of Daily Life Questionnaire [ADL]).

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If you have any questions, please do not hesitate to contact me at the telephone or email address listed directly below:

Contact person for the 510(k):
William A. Clementi, PharmD, FCP or Nancy D. Clementi, MD
Phone: (610) 527-2600
Secure Email: bill.clementi@clempharma.net or nancy.clementi@clempharma.net

Sincerely,

Nancy Clementi

Nancy D. Clementi, MD
Chief Medical Officer
US Agent for Cambridge Cognition

Encl: FDA Form 3514, Contents of Submission

Contents of Submission: 510(k) Cantab Mobile

1 Sections marked "N/A" are not applicable; an explanatory slip sheet is present for each N/A section in the electronic copy only. The paper copy only includes applicable section content.
2 Sections are grouped under an "Administrative" tab in the paper copy of the submission.
3 Sections are grouped under a "Statements" tab in the paper copy of the submission.
4 For ease of review, cited literature is included in the electronic submission copy.
5 Introductory signature pages are available upon request.
6 References are available upon request.
7 The majority of references present in the IFU are included electronically in either the Executive Summary (Section 10) or Device Description (Section 11). All other references are available upon request.
8 Cited literature is available upon request in NMI-054. Rock et. al, 2014 is provided, however, as an appendix in the electronic submission copy.

Form Approved: OMB No. 0910-0616. Expiration Date: 2/28/2018. See PRA Statement on page 2.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance

Under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. Name of Sponsor/Applicant/Submitter

Cambridge Cognition Ltd. US Agent: Clementi Associates Ltd.

2. Date of the Application/Submission Which This Certification Accompanies
05/12/2016

3. Address

Address 1 *(Street address, P.O. box, company name c/o)*
Tunbridge Court, Tunbridge Lane

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City
Bottisham

State/Province/Region
Cambridgeshire

Country
UK

ZIP or Postal Code
CB25 9TU

4. Telephone and Fax Numbers *(Include country code if applicable and area code)*

(Tel): (610) 527-2600

(Fax): 215-717-4698

PRODUCT INFORMATION

5. **For Drugs/Biologics:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s).
For Devices: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)

Cantab Mobile

Continuation Page for #5

APPLICATION / SUBMISSION INFORMATION

6. Type of Application/Submission Which This Certification Accompanies

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. Include IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/ Other Number *(If number previously assigned)*

If BLA was selected in item 6, provide Supplement Number

8. Serial Number Assigned to Application/Submission Which This Certification Accompanies

00000

CERTIFICATION STATEMENT / INFORMATION

9. Check only one of the following boxes *(See instructions for additional information and explanation)*

☒ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

Certification Statement / Information section continued on page 2

CERTIFICATION STATEMENT / INFORMATION *(Continued)*

10. If you checked box C, in number 9, provide the National Clinical Trial (NCT) Number(s) for any "applicable clinical trial(s)," under 42 U.S.C. § 282(J)(1)(a)(i), section 402(j)(1)(a)(i) of the Public Health Service Act, referenced in the application/ submission which this Certification accompanies. *(Add continuation page as necessary.)*

NCT Number(s): _____ _____ _____ _____ _____

Continuation Page for #10

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.

Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. Name and Title of the Person who Signs Number 15

Name	Title
Nancy D. Clementi M.D.	Chief Medical Officer, Clementi Associates Ltd.

12. Address

Address 1 *(Street address, P.O. box, company name c/o)*: 919 Conestoga Road		
Address 2 *(Apartment, suite, unit, building, floor, etc.)*: Building 3, Suite 312		
City: Rosemont	State/Province/Region: PA	
Country: USA		ZIP or Postal Code: 19010

13. Telephone and Fax Numbers *(Include country code if applicable and area code)*

(Tel): (610) 527-2600

(Fax): 215-717-4698

14. Date of Certification: 05/10/2016

15. Signature of Sponsor/Applicant/Submitter or an Authorized Representative *(Sign)*

Sign

Nancy D Clementi

This section applies only to requirements of the Paperwork Reduction Act of 1995.

*****DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*****

The burden time for this collection of information is estimated to average 15 minutes and 45 minutes (depending on the type of application/ submission) per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

CAMBRIDGE COGNITION

April 06, 2016

Appointment of US Agent

Original 510(k) Submission

Food and Drug Administration
Center for Devices and Radiological Health Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

RE: Cambridge Cognition Ltd., 510(k) – Cantab Mobile: General Correspondence: Appointment of US Agent

Dear Sir or Madam:

Pursuant to 21 CFR Chapter 1 §312.23(a§(ix), Cambridge Cognition Ltd., Tunbridge Court, Tunbridge Lane, Bottisham, Cambridge, CB25 9TU, United Kingdom hereby authorises Clementi and Associates, Ltd. (Clementi) to represent its interests in all matters concerning the Food and Drug Administration, as amended, related laws, and implementing regulations for the above referenced 510(k). Clementi and Associates, Ltd. will be responsible for submissions to, and authorised to receive correspondence from the FDA. Clementi and Associates, Ltd. will act as the sole authorised US Agent and all Agency communication should be maintained through Clementi.

Address:

Clementi and Associates Ltd.
919 Conestoga Road
Building 3, Suite 312
Rosemont, PA 19010

Contact person for the 510(k):

William A. Clementi, Pharm. D., FCP or
Nancy D. Clementi M.D
Phone: (610) 527-2600
Secure Email: bill.clementi@clempharma.net or
nancy.clementi@clempharma.net

CAMBRIDGE
COGNITION

There is no change in the 510(k) ownership. Cambridge Cognition Ltd. (United Kingdom) continues to be the owner of Cantab Mobile.

This change is effective per the date of this letter. The information is reflected on the enclosed form FDA Form 3514.

Sincerely,

Tina Bucknall
Contracts & Business Information Manager
Cambridge Cognition Ltd.

Cambridge Cognition Tunbridge Court, Tunbridge Lane, Bottisham, Cambridge, CB25 9TU, UK
t: +44 (0)1223 810700 f: +44 (0)1223 810701 info@camcog.com www.cambridgecognition.com

Appendix A

Contains Nonbinding Recommendations

Acceptance Checklist for Traditional 510(k)s

(Should be completed within 15 days of DCC receipt)

The following information is not intended to serve as a comprehensive review.
FDA recommends that the submitter include this completed checklist as part of the submission.

510(k)#: K **Date Received by DCC:**

Lead Reviewer:

Branch: **Division:** **Center/Office:**

Note: If an element is left blank on the checklist, it does not mean the checklist is incomplete; it means the reviewer did not assess the element during the RTA review and that the element will be assessed during substantive review.

Preliminary Questions

Answers in the shaded blocks indicate consultation with a Center advisor is needed. (Boxes checked in this section represent FDAs preliminary assessment of these questions at the time of administrative review.)

	Yes	No	N/A
1. Is the product a device (per section 201(h) of the FD&C Act) or a combination product (per 21 CFR 3.2(e)) with a device constituent part subject to review in a 510(k)? If it appears not to be a device (per section 201(h) of the FD&C Act) or such a combination product, or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Product Jurisdiction Liaison to determine the appropriate action, and inform division management. *Provide a summary of the Jurisdictional Officer's/Liaison's determination.* If the product does not appear to be a device or such a combination product, mark "No."	☑	☐	
Comments:			
2. Is the submission with the appropriate Center? If the product is a device or a combination product with a device constituent part, is it subject to review by the Center in which the submission was received? If you believe the submission is not with the appropriate Center or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Product Jurisdiction Liaison to determine the appropriate action and inform your division management. *Provide a summary of the Jurisdictional Officer's/Liaison's determination.* If submission should not be reviewed by your Center mark "No."	☑	☐	
Comments:			

3. If a Request for Designation (RFD) was submitted for the device or combination product with a device constituent part and assigned to your center, identify the RFD # and confirm the following: **a) Is the device or combination product the same (e.g., design, formulation) as that presented in the RFD submission?** **b) Are the indications for use for the device or combination product identified in the 510(k) the same as those identified in the RFD submission?** If you believe the product or the indications presented in the 510(k) have changed from the RFD, or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Product Jurisdiction Liaison to determine the appropriate action and inform your division management. *Provide summary of Jurisdictional Officer's/Liaison's determination.* If the answer to either question above is no, mark "No." If there was no RFD, mark "N/A."	☐	☐	☑
Comments:			
4. Is this device type eligible for a 510(k) submission? If a 510(k) does not appear to be appropriate (e.g., Class III type and PMA required, or Class I or II type and 510(k)-exempt), you should consult with the CDRH 510(k) Program Director or appropriate CBER staff during the acceptance review. If 510(k) is not the appropriate regulatory submission, mark "No."	☑	☐	
Comments:			
5. Is there a pending PMA for the same device with the same indications for use? If yes, consult division management and the CDRH 510(k) Program Director or appropriate CBER staff to determine the appropriate action.	☐	☑	
Comments:			
6. If clinical studies have been submitted, is the submitter the subject of an Application Integrity Policy (AIP)? If yes, consult with the CDRH Office of Compliance/Division of Bioresearch Monitoring (OC/DBM) or CBER Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Bioresearch Monitoring Branch (OCBQ/DIS/BMB) to determine the appropriate action. Check on web at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm. If no clinical studies have been submitted, mark "N/A."	☐	☐	☑
Comments:			

- **If the answer to 1 or 2 appears to be "No," then stop review of the 510(k) and issue the "Original Jurisdictional Product" letter.**
- **If the answer to 3a or 3b appears to be "No," then stop the review and contact the CDRH Jurisdictional Officer or CBER Office of Jurisdiction Liaison.**

- **If the answer to 4 is "No", the lead reviewer should consult division management and other Center resources to determine the appropriate action.**
- **If the answer to 5 is "Yes," then stop review of the 510(k), contact the CDRH 510(k) Staff and PMA Staff, or appropriate CBER staff.**
- **If the answer to 6 is "Yes," then contact CDRH/OC/DBM or CBER/OCBQ/DIS/BMB, provide a summary of the discussion with DBM or BMB Staff, and indicate their recommendation/action.**

Organizational Elements Failure to include these items should not result in an RTA designation.				
***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**		**Yes**	**No**	***Page #**
1.	Submission contains a Table of Contents.	☑	☐	3-3
2.	Each section is labeled (e.g., headings or tabs designating Device Description section, Labeling section, etc.).	☑	☐	
3.	All pages of the submission are numbered. *All pages should be numbered in such a manner that information can be referenced by page number. This may be done either by consecutively numbering the entire submission, or numbering the pages within a section (e.g., 12-1, 12-2…).*	☑	☐	
4.	Type of 510(k) is identified (i.e., Traditional, Abbreviated, or Special) *If type of 510(k) is not designated, review as a Traditional 510(k).*	☑	☐	2-1
Comments:	Page numbering was not added to FDA forms; security permissions do not allow altering the forms in this way. The page numbering is, however, accounted for in the table of contents.			

Elements of a Complete Submission (RTA Items) **(21 CFR 807.87 unless otherwise indicated)** Submission should be designated RTA if not addressed
• Any "No" answer will result in a "Refuse to Accept" decision; however, FDA staff has discretion to determine whether missing items are needed to ensure that the submission is administratively complete to allow the submission to be accepted or to request missing checklist items interactively from submitters during the RTA review. • Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
A.	**Administrative**						
	1.	All content used to support the submission is written in English (including translations of test reports, literature articles, etc.).		☑	☐		
		Comments:					
	2.	Submission identifies the following (FDA recommends use of the CDRH Premarket Review Submission Cover Sheet form [Form 3514]):					2-1
		a.	Device trade/proprietary name	☑	☐		
		b.	Device class and panel or Classification regulation or Statement that device has not been classified with rationale for that conclusion	☑	☐		
		Comments:					
	3.	Submission contains an Indication for Use Statement with Rx and/or OTC designated (see also 21 CFR 801.109, and FDA's guidance "Alternative to Certain Prescription Devices Labeling Requirements.") *See recommended format (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM360431.pdf).*		☑	☐		4-1
		Comments:					
	4.	Submission contains a 510(k) Summary or 510(k) Statement. *Refer to 21 CFR 807.92 and 21 CFR 807.93 for contents of 510(k) Summary and Statement, respectively. Adequacy of the content will be assessed during substantive review.*		☑	☐		5-1
		Comments:					
	5.	Submission contains a Truthful and Accuracy Statement per 21 CFR 807.87(k). *See recommended format (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142707.htm).*		☑	☐		6-1
		Comments:					

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
	6.		Submission is a Class III 510(k) Device. *Select "N/A" only if submission is not a Class III 510(k).*	☐		☑	
		a.	Contains Class III Summary and Certification *See recommended content (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142662.htm). Select "N/A" only if submission is not a Class III 510(k).*	☐	☐	☑	
			Comments:				
	7.		Submission contains clinical data. *Select "N/A" if the submission does not contain clinical data. If "N/A"is selected, parts a and b below are omitted from the checklist.*	☐		☑	
		a.	Submission includes completed Financial Certification (FDA Form 3454) or Disclosure (FDA Form 3455) information for each covered clinical study included in the submission. *Select "N/A" if the submitted clinical data is not a "covered clinical study" as defined in the Guidance for Industry-Financial Disclosures by Clinical Investigators.*	☐	☐	☐	
		b.	Submission includes completed Certification of Compliance with requirements of ClinicalTrials.gov Data Bank (FDA Form 3674) (42 U.S.C. 282(j)(5)(B)) for each applicable device clinical trial included in the submission. *Select "N/A" if the submitted clinical data is not an "applicable device clinical trial" as defined in Title VIII of FDAAA, Sec. 801(j)*	☑	☐	☐	3-4
			Comments: FDA form 3674 is included however, "A" is checked for Question 9 (Certification Statement).				
	8.		The submission identifies prior submissions for the same device included in the current submission (e.g., submission numbers for a prior not substantially equivalent [NSE] determination, prior deleted or withdrawn 510(k), Pre-Submission, IDE, PMA, etc.). **OR** States that there were no prior submissions for the subject device. *Prior submissions (or no prior submissions) for this device should be included in Section F (prior related submissions) of the CDRH Premarket Review Submission Cover Sheet form (Form 3514).*	☑	☐		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
		This information may also be included in the Cover Letter (i.e., as a statement that there were no prior submissions for the device or a listing of the number(s) of the prior submissions).					
		a.	If there were prior submissions, the submitter has identified where in the current submission any issues related to a determination of substantial equivalence from prior submissions for this device are addressed. *To address this criterion, it is recommended that the submission include a separate section with the prior submission number(s), a copy of the FDA feedback (e.g., letter, meeting minutes), and a statement of how or where in the submission this prior feedback was addressed. Note that adequacy of how the feedback was addressed will be assessed during the substantive review.* *Select "N/A" if the submitter states there were no prior submissions.*	☐	☐	☑	
		Comments:					
B.	**Device Description**						
	9.	The device has a device-specific guidance document, special controls document, and/or requirements in a device-specific regulation regarding device description that is applicable to the subject device. *If "N/A"is selected, parts a and b below are omitted from the checklist.*		☐		☑	
		a.	The submission addresses device description recommendations outlined in the device-specific guidance. **OR** The submission provides an alternative approach intended to address the applicable statutory and/or regulatory criteria. *Select "N/A" if there is no applicable device-specific guidance. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how recommendations in a device-specific guidance, etc., have been addressed should be assessed during the substantive review.*	☐	☐	☐	

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
		b.	The submission includes device description information that addresses relevant mitigation measures set forth in a special controls document or device-specific regulation applicable to the device. **OR** The submission uses alternative mitigation measures and provides rationale why the alternative measures provide an equivalent assurance of safety and effectiveness. *Select "N/A" if there is no applicable special controls document or device-specific regulation. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how such mitigation measures have been addressed should be assessed during the substantive review.*	☐	☐	☐	
		Comments:					
	10.	Descriptive information is present and consistent within the submission (e.g., the device description section is consistent with the device description in the labeling).		☑	☐		11-1
		Comments:					
	11.	The submission includes descriptive information for the device, including the following:					11-1
		a.	A description of the principle of operation or mechanism of action for achieving the intended effect.	☑	☐		
		b.	A description of proposed conditions of use, such as surgical technique for implants; anatomical location of use; user interface; how the device interacts with other devices; and/or how the device interacts with the patient.	☑	☐		
		c.	A list and description of each device for which clearance is requested. *Select "N/A" if there is only one device or model. "Device" may refer to models, part numbers, various sizes, etc.*	☐	☐	☑	
		d.	Submission contains representative engineering drawing(s), schematics, illustrations, photos and/or figures of the device. **OR**	☑	☐		11-25

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
			Submission includes a statement that engineering drawings, schematics, etc. are not applicable to the device (e.g., device is a reagent and figures are not pertinent to describe the device). *In lieu of engineering drawings, schematics, etc. of each device to be marketed, "representative" drawings, etc. may be provided, where "representative" is intended to mean that the drawings, etc. provided capture the differences in design, size, and other important characteristics of the various models, sizes, or versions of the device(s) to be marketed.*				
		Comments: Only third-party hardware, on which the medical device software runs, is in contact with patient.					
	12.	Device is intended to be marketed with multiple components, accessories, and/or as part of a system. *Select "N/A" if the device is not intended to be marketed with multiple components, accessories, and/or as part of a system. If "N/A"is selected, parts a-c below are omitted from the checklist.*		☐		☑	
		a.	Submission includes a list of all components and accessories to be marketed with the subject device.	☐	☐		
		b.	Submission includes a description (as detailed in item 11a., 11b., and 11d. above) of each component or accessory. *Select "N/A" if the component(s)/accessory(ies) has been previously cleared, or is exempt, and the proposed indications for use are consistent with the cleared indications.*	☐	☐	☐	
		c.	A 510(k) number is provided for each component or accessory that received a prior 510(k) clearance **AND** A statement is provided that identifies components or accessories that have not received prior 510(k) clearance.	☐	☐		
		Comments:					
C.	**Substantial Equivalence Discussion**						10-9
	13.	Submitter has identified a predicate device(s), including the following information:					
		a.	Predicate device identifier provided (e.g., 510(k) number, de	☑	☐		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
			novo number, reclassified PMA number, regulation number if exempt or statement that the predicate is a preamendment device). For predicates that are preamendments devices, information is provided to document preamendments status. *Information regarding documenting preamendment status is available online (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/MedicalDeviceQualityandCompliance/ucm379552.htm).*				
		b.	The identified predicate(s) is consistent throughout the submission (e.g., the predicate(s) identified in the Substantial Equivalence section is the same as that listed in the 510(k) Summary (if applicable) and that used in comparative performance testing.	☑	☐		
		Comments:					
	14.	Submission includes a comparison of the following for the predicate(s) and subject device and a discussion why any differences between the subject and predicate(s) do not impact safety and effectiveness [see section 513(i)(1)(A) of the FD&C Act and 21 CFR 807.87(f)] *See "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" guidance document for more information on comparing intended use and technological characteristics.*					
		a.	Indications for use *If there are no differences between the subject device and the predicate(s) with respect to indications and intended use, this should be explicitly stated.*	☑	☐		
		b.	Technology, including features, materials, and principles of operation *Examples of technological characteristics include, but are not limited to design, features, materials, energy source, and principle of operation.* *FDA recommends a tabular format for comparing technological characteristics. Any characteristic that is the*	☑	☐		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
			same as the predicate(s) should be explicitly stated. Differences in technological characteristics should be identified and a rationale provided why they do not raise different questions of safety and effectiveness.				
		Comments:					
D.	**Proposed Labeling (see also 21 CFR parts 801 and 809 as applicable)**						13-1
	15.	Submission includes proposed package labels and labeling (e.g., instructions for use, package insert, operator's manual).		☑	☐		
		a.	Indications for use are stated in labeling and are identical to Indications for Use form and 510(k) Summary (if 510(k) Summary provided)	☑	☐		
		b.	Labeling includes: - Statements of conditions, purposes or uses for which the device is intended (e.g., hazards, warnings, precautions, contraindications) (21 CFR 801.5) **AND** - Includes adequate directions for use (see 21 CFR 801.5) **OR** - Submission states that device qualifies for exemption per 21 CFR 801 Subpart D	☑	☐		
		Comments:					
	16.	Labeling includes name and place of business of the manufacturer, packer, or distributor (21 CFR 801.1)		☑	☐		
		Comments:					
	17.	Labeling includes the prescription statement (see 21 CFR 801.109(b)(1)) or Rx Only symbol (see also Section 502(a) of the FD&C Act and FDA's guidance "Alternative to Certain Prescription Device Labeling Requirements"). *Select "N/A" if not indicated for prescription use.*		☐	☐	☑	
		Comments:					

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
	18.	The device has a device-specific guidance document, special controls document, and/or requirements in a device-specific regulation regarding labeling that is applicable to the subject device. *If "N/A"is selected, parts a and b below are omitted from the checklist.*		☐		☑	
		a.	The submission addresses labeling recommendations outlined in the device-specific guidance. **OR** The submission provides an alternative approach intended to address the applicable statutory and/or regulatory criteria. *Select "N/A" if there is no applicable device-specific guidance. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how recommendations in a device-specific guidance, etc., have been addressed should be assessed during the substantive review.*	☐	☐	☐	
		b.	The submission includes labeling information that addresses relevant mitigation measures set forth in a special controls document or device-specific regulation applicable to the device. **OR** The submission uses alternative mitigation measures and provides rationale why the alternative measures provide an equivalent assurance of safety and effectiveness. *Select "N/A" if there is no applicable special controls document or device-specific regulation. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how such mitigation measures have been addressed should be assessed during the substantive review.*	☐	☐	☐	
		Comments:					
	19.	If the device is an in vitro diagnostic device, provided labeling includes all applicable information required per 21 CFR 809.10. Select "N/A" if not an in vitro diagnostic device.		☐	☐	☑	

		Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**	**Yes**	**No**	**N/A**	***Page #**
		Comment:				
E.	**Sterilization** *If an in vitro diagnostic (IVD) device and sterilization is not applicable, select "N/A." The criteria in this section will be omitted from the checklist if "N/A" is selected.*				☐	
	Submission states that the device, and/or accessories, and/or components are: (*one of the below must be checked*) ☐ Provided sterile, intended to be single-use ☐ Requires processing during its use-life ☐ Non-sterile when used (and no processing required) ☑ Information regarding the sterility status of the device is not provided (if this box is checked, please also check one of the two boxes below) ☑ Sterility status not needed for this device (e.g., software-only device) ☐ Sterility status needed or need unclear This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination. *If "non-sterile when used" or "not provided and not needed" is selected, the sterility-related criteria below are omitted from the checklist.* *If information on sterility status is not provided, and it is needed or the need for this information is unclear, select "No."* *The "Requires processing during its use-life" option refers to devices falling into one of the four categories below:* • *Supplied sterile and requires reprocessing prior to subsequent patient use* • *Supplied non-sterile and requires user to process the device for initial use, as well as to reprocess the device after each use* • *Reusable medical device (single-user) reprocessed between each use* • *Single-use medical devices initially supplied as non-sterile to the user, and requiring the user to process the device prior to its use* *Please refer to the guidance document titled "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling" for additional information.*		☐		
	Comments:					
	20.	Assessment of the need for cleaning and subsequent disinfection				

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
			or sterilization information.				
		a.	Identification of device, and/or accessories, and/or components that are provided sterile. *Select "N/A" if no part of the device, accessories, or components is provided sterile.*	☐	☐	☑	
		b.	Identification of device, and/or accessories, and/or components that are end user sterilized or disinfected. *Select "N/A" if no part of the device, accessories, or components is end user sterilized or disinfected.*	☐	☐	☑	
		c.	Identification of device, and/or accessories, and/or components that are reusable. *Select "N/A" if no part of the device, accessories, or components is reusable.*	☐	☐	☑	
		Comments:					
	21.	If the device, and/or accessory, and/or a component is provided sterile: *Select "N/A" if no part of the device, accessories, or components is provided sterile, otherwise complete a-f below.*				☑	
		a.	Sterilization method is stated for each component (including dose for radiation sterilization)	☐	☐		
		b.	A description of method to validate the sterilization parameters is provided for each proposed sterilization method (e.g., half-cycle method and full citation of FDA-recognized standard, including date). *Note: the sterilization validation report is not required.*	☐	☐		
		c.	For devices sterilized using chemical sterilants such as ethylene oxide (EO) and hydrogen peroxide, submission states maximum levels of sterilant residuals remaining on the device and sterilant residual limits. *Select "N/A" if not sterilized using chemical sterilants.*	☐	☐	☐	
		d.	Sterility Assurance Level (SAL) stated	☐	☐		
		e.	Submission includes description of packaging	☐	☐		
		f.	For products labeled "non-pyrogenic," a description of the method used to make the determination stated (e.g., limulus	☐	☐	☐	

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
			amebocyte lysate [LAL]). *Select "N/A" if not labeled "non-pyrogenic."*				
		Comments:					
	22.	If the device, and/or accessory, and/or a component is reusable or end user sterilized or disinfected: *Select "N/A" if no part of the device, accessories, or components are reusable or end user sterilized or disinfected, otherwise complete a-d below.*				☑	
		a.	Cleaning method is provided in labeling for each device, and/or accessory, and/or component. *Select "N/A" if not reusable and does not need cleaning prior to disinfection or sterilization*	☐	☐	☐	
		b.	Disinfection method is provided in labeling for each device, and/or accessory, and/or component. *Select "N/A" if not disinfected (i.e., undergoes terminal sterilization) prior to use*	☐	☐	☐	
		c.	Sterilization method is provided in labeling for each device and/or accessory, and/or component. *Select "N/A" if not sterilized (i.e., undergoes disinfection) prior to use*	☐	☐	☐	
		d.	Device types in this submission are listed in Appendix E of the FDA's guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling." *Device types identified in Appendix E of the reprocessing guidance represent devices posing a greater likelihood of microbial transmission and represent a high risk of infection. Select "N/A" if the device type in the submission is not included in Appendix E of the reprocessing guidance.*	☐		☐	
			i. If device types in this submission are included in Appendix E of the reprocessing guidance, the submission includes protocols and test reports for validating the reprocessing instructions. *Select "N/A" if the device type in the submission is not included in Appendix E of the reprocessing guidance.*	☐	☐	☐	
		Comments:					

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
	23.	The device has a device-specific guidance document, special controls document, and/or requirement in a device-specific regulation regarding sterility and/or reprocessing that is applicable to the subject device *If "N/A"is selected, parts a and b below are omitted from the checklist.*		☐		☑	
		a.	The submission addresses sterility and/or reprocessing recommendations outlined in the device-specific guidance. **OR** The submission provides an alternative approach intended to address the applicable statutory and/or regulatory criteria. *Select "N/A" if there is no applicable device-specific guidance. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how recommendations in a device-specific guidance, etc., have been addressed should be assessed during the substantive review.*	☐	☐	☐	
		b.	The submission includes sterility and/or reprocessing information that addresses relevant mitigation measures set forth in a special controls document or device-specific regulation applicable to the device. **OR** The submission uses alternative mitigation measures and provides rationale why the alternative measures provide an equivalent assurance of safety and effectiveness. *Select "N/A" if there is no applicable special controls document or device-specific regulation. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how such mitigation measures have been addressed should be assessed during the substantive review.*	☐	☐	☐	
		Comments:					
F.	**Shelf-Life**						
	24.	Proposed shelf life/ expiration date stated		☑	☐		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.			Yes	No	N/A	*Page #
		OR Statement that shelf-life is not applicable because of low likelihood of time-dependent product degradation				
		Comments: The device does not have a restricted shelf life; ongoing support of manufacturer is required, however. See Section 1 of the Device Description for additional details.				
	25.	For a sterile device, submission includes summary of methods used to establish that device packaging will maintain a sterile barrier for the entirety of the proposed shelf-life. *Select "N/A" if the device is not provided sterile.*	☐	☐	☑	
		Comments: See IFU (pg 1) for santizing instructions performed.				
	26.	Submission includes summary of methods used to establish that device performance is maintained for the entirety of the proposed shelf-life (e.g., mechanical properties, coating integrity, pH, osmolality, etc.). **OR** Statement why performance data is not needed to establish maintenance of device performance characteristics over the shelf-life period.	☑	☐		
		Comments: The device does not have a restricted shelf life; ongoing support of manufacturer is required, however. See Section 1 of the Device Description for additional details.				
G.	**Biocompatibility** *If an in vitro diagnostic (IVD) device, select "N/A." The criteria in this section will be omitted from the checklist if "N/A" is selected.*				☑	
	Submission states that there: (*one of the below must be checked*) ☐ Are direct or indirect patient-contacting components ☐ Are no direct or indirect patient-contacting components ☐ Information regarding patient contact status of the device is not provided (if this box checked, please also check one of the two boxes below) ☐ Patient contact information not needed for this device (e.g., software-only device) ☐ Patient contact information is needed or need unclear This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination. *If "are no" or "not provided and not needed" is selected, the biocompatibility-*			☐		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**			**Yes**	**No**	**N/A**	***Page #**
	related criteria below are omitted from the checklist. If information on the patient-contact status is not provided, and contact information is needed or its contact status is unclear, select "No." *An example of a direct patient-contacting device would be an implant that has direct contact with patient tissues during use. An example of an indirect patient-contacting device would be fluid entering the patient's body following passing through device/device components not in direct contact with the patient.*					
	Comments:					
	27.	Submission includes a list identifying each patient-contacting device component (e.g., implant, delivery catheter) and associated materials of construction for each component, including identification of color additives, if present.	☐	☐		
		Comments:				
	28.	Submission identifies contact classification (e.g., surface-contacting, less than 24 hour duration) for each patient-contacting device component (e.g., implant, delivery catheter).	☐	☐		
		Comments:				
	29.	Biocompatibility assessment of patient-contacting components Submission includes: Test protocol (including identification and description of test article), methods, pass/fail criteria, and results provided for each completed test. **OR** A statement that biocompatibility testing is not needed with a rationale (e.g., materials and manufacturing/processing are identical to the predicate).	☐	☐		
		Comments:				
H.	**Software**					16-1
	Submission states that the device: (*one of the below must be checked*) ☑ Does contain software/firmware ☐ Does not contain software/firmware			☐		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**			**Yes**	**No**	**N/A**	***Page #**
	☐ Information on whether device contains software/firmware is not provided (if this box checked, please also check one of the two boxes below) ☐ Software/firmware information not needed for this device (e.g., surgical suture, condom) ☐ Software/firmware information is needed or need unclear This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination. *If "does not contain" or "not provided and not needed" is selected, the software-related criteria below are omitted from the checklist. If information on software is not provided, and this information is needed or the need is unclear, select "No."*					
	Comments:					
	30.	Submission includes a statement of software level of concern and rationale for the software level of concern	☑	☐		
		Comments:				
	31.	All applicable software documentation provided based on level of concern identified by the submitter, as described in Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, or the submission includes information to establish that the submitter has otherwise met the applicable statutory or regulatory criteria through an alternative approach (i.e., the submitter has identified an alternate approach with a rationale). *Note: This element is also applicable to non-internally generated or off-the-shelf (OTS) software used in the device.*	☑	☐		
		Comments:				
I.	**Electrical Safety and EMC**					
	Electrical Safety: Submission states that the device: (*one of the below must be checked*) ☐ Does require electrical safety evaluation ☑ Does not require electrical safety evaluation ☐ Information on whether device requires electrical safety evaluation not			☐		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**			**Yes**	**No**	**N/A**	***Page #**
	provided (if this box checked, please also check one of the two boxes below) ☐ Electrical safety information not needed for this device (e.g., surgical suture, condom) ☐ Electrical safety information needed or need unclear This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination. *If "does not require" or "not provided and not needed" is selected, the electrical safety criteria below are omitted from the checklist. If information on electrical safety is not provided, and it is needed or the need for this information is unclear, select "No."*					
	Comments:					
	32.	Submission includes evaluation of electrical safety (e.g., per IEC 60601-1, or equivalent FDA-recognized standard, and if applicable, a device-specific standard). **OR** Submission includes electrical safety evaluation using methods or standards that are not FDA-recognized and submission includes information to establish that the submitter has otherwise met the applicable statutory or regulatory criteria through this alternative approach (i.e., the submitter has identified alternate methods or standards with a rationale).	☐	☐		
		Comments:				
	EMC: Submission states that the device: (*one of the below must be checked*) ☐ Does require EMC evaluation ☑ Does not require EMC evaluation ☐ Information on whether device requires EMC evaluation not provided (if this box checked, please also check one of the two boxes below) ☐ EMC information not needed for this device (e.g., surgical suture, condom) ☐ EMC information needed or need unclear This information will determine whether and what type of additional			☐		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.				Yes	No	N/A	*Page #
	information may be necessary for a substantial equivalence determination. *If "does not require" or "not provided and not needed" is selected, the EMC criteria below are omitted from the checklist. If information on EMC is not provided, and it is needed or the need for this information is unclear, select "No."*						
	Comments:						
	33.	Submission includes evaluation of electromagnetic compatibility (e.g., per IEC 60601-1-2 or equivalent FDA-recognized standard and if applicable, a device-specific standard). **OR** Submission includes electromagnetic compatibility evaluation using methods or standards that are not FDA-recognized and submission includes information to establish that the submitter has otherwise met the applicable statutory or regulatory criteria through this alternative approach (i.e., the submitter has identified alternate methods or standards with a rationale).		☐	☐		
		Comments:					
J.	**Performance Data General** *If an in vitro diagnostic (IVD) device, select "N/A." The criteria in this section will be omitted from the checklist if "N/A" is selected. Performance data criteria relating to IVD devices is addressed in Section K.*					☐	
	Comments:						
	34.	Full test report is provided for each completed test. A full test report includes: objective of the test, description of the test methods and procedures, study endpoint(s), pre- defined pass/fail criteria, results summary, conclusions. *Full test reports provided for all completed tests/evaluations (e.g., bench evaluations, comparative performance tests, etc.). Select "N/A" if the submission does not include performance data.*		☑	☐	☐	20-1
		a.	Submission includes an explanation of how the data generated from each test report supports a finding of substantial equivalence (e.g., comparison to predicate device testing, dimensional analysis, etc.). *Select "N/A" if the submission does not include performance*	☐	☐	☑	

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
			data.				
		Comments:					
	35.	The device has a device-specific guidance document, special controls document, and/or requirement in a device-specific regulation regarding performance data that is applicable to the subject device *If "N/A"is selected, parts a and b below are omitted from the checklist.*		☐		☑	
		a.	The submission addresses performance data recommendations outlined in the device-specific guidance. **OR** The submission provides an alternative approach intended to address the applicable statutory and/or regulatory criteria. *Select "N/A" if there is no applicable device-specific guidance. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how recommendations in a device-specific guidance, etc., have been addressed should be assessed during the substantive review.*	☐	☐	☐	
		b.	The submission includes performance data that addresses relevant mitigation measures set forth in a special controls document or device-specific regulation applicable to the device. **OR** The submission uses alternative mitigation measures and provides rationale why the alternative measures provide an equivalent assurance of safety and effectiveness. *Select "N/A" if there is no applicable special controls document or device-specific regulation. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how such mitigation measures have been addressed should be assessed during the substantive review.*	☐	☐	☐	
		Comments:					

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
	36.	If literature is referenced in the submission, submission includes: *Select "N/A" if the submission does not reference literature. If "N/A"is selected, parts a and b below are omitted from the checklist.* *Note that the applicability of the referenced article to support a substantial equivalence finding should be assessed during the substantive review; only the presence of a discussion is required to support acceptance.*				☐	
		a.	Legible reprints or a summary of each article.	☑	☐		
		b.	Discussion of how each article is applicable to support the substantial equivalence of the subject device to the predicate.	☑	☐		
		Comments: The articles are not added with the intention of supporting substantial equivalence to the predicate.					
	37.	For each completed aninmal study,the submission provides the following: *Select "N/A" if no animal study was conducted. If "N/A"is selected, parts a-c below are omitted from the checklist. Note that this section does not address biocompatibility evaluations, which are assessed in Section G of the checklist.*				☑	
		a.	Submission includes a study protocol which includes all elements as outlined in 21 CFR 58.120	☐	☐		
		b.	Submission includes final study report which includes all elements outlined in 21 CFR 58.185	☐	☐		
		c.	Submission contains a statement that the study was conducted in compliance with applicable requirements in the GLP regulation (21 CFR Part 58), or, if the study was not conducted in compliance with the GLP regulation, the submission explains why the noncompliance would not impact the validity of the study data provided to support a substantial equivalence determination.	☐	☐		
		Comments:					
K.	**Performance Characteristics – In Vitro Diagnostic Devices Only (see also 21 CFR 809.10(b)(12))**						
	Submission indicates that device: (*one of the below must be checked*) ☐ Is an in vitro diagnostic device						

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
	☑ Is not an in vitro diagnostic device *If "is not" is selected, the performance data-related criteria below are omitted from the checklist.*						
	38.	Submission includes the following studies, as appropriate for the device type, including associated protocol descriptions, study results and line data:					
		a.	Precision/reproducibility	☐	☐	☐	
		b.	Accuracy (includes as appropriate linearity; calibrator or assay traceability; calibrator and/or assay stability protocol and acceptance criteria; assay cut-off; method comparison or comparison to clinical outcome; matrix comparison; and clinical reference range or cutoff.	☐	☐	☐	
		c.	Sensitivity (detection limits, LoB, LoD, LoQ where relevant for the device type).	☐	☐	☐	
		d.	Analytical specificity	☐	☐	☐	
		Comments:					
	39.	The device has a device-specific guidance document, special controls document, and/or requirement in a device-specific regulations regarding performance data that is applicable to the subject device. *If "N/A"is selected, parts a and b below are omitted from the checklist.*		☐	☐	☐	
		a.	The submission addresses performance data recommendations outlined in the device-specific guidance. **OR** The submission provides an alternative approach intended to address the applicable statutory and/or regulatory criteria. *Select "N/A" if there is no applicable device-specific guidance. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how recommendations in a device-specific guidance, etc., have been addressed should be assessed during the substantive review.*	☐	☐	☐	
		b.	The submission includes performance data that addresses	☐	☐	☐	

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.				Yes	No	N/A	*Page #
			relevant mitigation measures set forth in a special controls document or device-specific regulation applicable to the device. **OR** The submission uses alternative mitigation measures and provides rationale why the alternative measures provide an equivalent assurance of safety and effectiveness. *Select "N/A" if there is no applicable special controls document or device-specific regulation. Select "No" if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how such mitigation measures have been addressed should be assessed during the substantive review.*				
		Comments:					

Decision: **Accept_____ Refuse to Accept_____**

If Accept, notify the applicant

If Refuse to Accept, notify applicant electronically and include a copy of this checklist.

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Chief Sign-Off (digital signature optional)*	
Division Sign-Off (digital signature optional)*	

*Branch and Division review of checklist and concurrence with decision required. Branch and Division digital signature optional.

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CAMBRIDGE COGNITION

April 08, 2016

Premarket Notification
510(k) Statement
As Required by
21 CFR 807.93]

Original 510(k) Submission
Cantab Mobile

(As Required By 21 CFR 807.93)
I certify that, in my capacity as Director of Technical Operations of Cambridge Cognition Ltd., I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61.

(Signature of Certifier)

Ricky Dolphin

(Typed Name)

08-APR-2016

(Date)

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Cambridge Cognition Holdings plc, a company registered in England and Wales, Registered Number 04338746

CAMBRIDGE COGNITION

April 29th, 2016

Premarket Notification Truthful and Accurate Statement as Required by 21 CFR 807.87(k)]

Original 510(k) Submission
Cantab Mobile

I certify that, in my capacity as Director of Technical Operations of Cambridge Cognition Ltd., I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

(Signature)

Ricky Dolphin
(Typed Name)

29TH APRIL 2016
(Date)

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Cantab Mobile

7. Class III Summary and Certification Statement

Cantab Mobile is not classified as a class III device. Therefore, this section is not applicable.

Cantab Mobile

8. Financial Certification or Disclosure Statement

No clinical studies were conducted as a part of this 510(k) submission. Therefore, this section is not applicable.

CAMBRIDGE COGNITION

Cantab Mobile

9. Declaration of Conformity and Summary Reports

This is a traditional 510(k) submission. This section is not applicable.

Cantab Mobile

10. Executive Summary

Product Name: Cantab Mobile
Indication: Assess Memory in Patients Aged 50 to 90 Years

Sponsor

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale – Cognition
ADHD	Attention deficit hyperactivity disorder
ADL	Activities for Daily Living Questionnaire
CANTAB	Cambridge Neuropsychology Test Automated Battery
CAPA	Corrective and Preventative Action
DLB	Dementia with Lewy Bodies
FDS	Functional Design Specification
GDS	Geriatric Depression Screening Questionnaire
HD	Huntington's disease
ID	Identification
IFU	Instructions for Use
MCI	Mild Cognitive Impairment
MEDDEV	Medical Device guidance document
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association
PAL	Paired Associates Learning
PIN	Personal Identification Number
RS	Requirements Specification
SCM	Software Configuration Management
SDLC	Software Development Life Cycle
SDS	Software Design Specification
SOP	Standard Operating Procedure
SOUP	Software Of Unknown Provenance
QD	Questionable dementia
QMS	Quality Management System
VMP	Validation Master Plan

1 BACKGROUND

1.1 Information on Dementia and Relevancy of Testing

It is estimated that dementia currently affects approximately 37 million people worldwide and, as the population ages, these prevalence rates can be expected to increase substantially. In addition to the devastating personal impact that a diagnosis of dementia may have upon the lives of patients and their caregivers, there is also a financial burden. The total monetary cost of dementia in 2010 was between $157 billion and $215 billion (Hurd et al., 2013).

Current criteria for the diagnosis of probable AD stipulates deterioration in two or more areas of cognition including memory of sufficient magnitude to interfere with work or social function. Critically however, substantial neuropathological change may have occurred before clinically significant symptoms (Jack et al. 2010; Jansen et al. 2015) appear. Thus, commencing treatment of AD at the time of clinical diagnosis (whether with cholinergic / glutamatergic drugs, anti-amyloid deposit agents or other putative disease modifying agents) may be sub-optimal or even ineffective because of the advanced stage of neurodegeneration at that time. The identification of cognitive tests that are sensitive to early pathological changes would facilitate the diagnosis of patients in a 'prodromal' state (i.e., those in whom the pathological process is present but whose symptoms are currently sub-clinical). Such early detection would serve to maximize the potential therapeutic benefit of treatment, enhance patient quality of life and, in so doing, reduce the burden on residential and nursing care services. Consequently, a very high therapeutic and economic premium is placed on the early detection and diagnosis of AD.

The CANTAB (Cambridge Neuropsychology Test Automated Battery) PAL (Paired Associates Learning) requires patients to learn and remember abstract visual patterns associated with various locations on a touch sensitive computer screen. See Section 3 below for additional detail.

A series of independent studies have demonstrated that Cantab PAL measures of visuospatial associative learning and semantic memory are sensitive in detecting the earliest signs of prodromal Alzheimer's disease (up to 32 months prior to clinical diagnosis) both in memory clinic attendees (Fowler et al., 1995, Fowler et al., 1997; Fowler et al., 2002; Swainson et al., 2001; Blackwell et al., 2004) and in community dwelling cohorts of individuals classified as asymptomatic using current clinical measures (De Jager et al., 2002); De Jager et al., 2005).

Further studies using Cantab PAL have confirmed it to be of utility in early and differential diagnosis in AD on a case-by-case basis. The Cantab PAL performance of patients with mild AD was impaired relative to both demographically-matched healthy controls (Sahakian et al., 1988) and to individuals with Frontal Variant Fronto-Temporal Dementia (Lee et al, 2003). Of critical importance, Cantab PAL was also found to be relatively insensitive to major unipolar depression (only 7 percent of scores of patients with Depression and Alzheimer's disease fell within an overlapping range) (Swainson et al., 2001). This result suggests that Cantab PAL is of utility in the differential diagnosis of early AD and depression (unlike word recall tests – see O'Carroll et al., 1997). Unlike ADAS-COG, performance on Cantab PAL

was also found to correlate significantly with subsequent deterioration in global cognitive function. Furthermore, in a group of individuals with 'questionable dementia', baseline Cantab PAL results revealed an apparent subgroup of patients who performed like AD patients. In a follow up study, Blackwell et al. (2004) showed that by taking into account age and performance on one other neuropsychological test (The Graded Naming Test [McKenna & Warrington, 1980]), Cantab PAL gave a 100% distinction between patients with questionable dementia who either did or did not convert to probable AD (NINCDS-ADRDA criteria) 32 months after baseline testing (see also De Jager et al., 2002). These studies also revealed that the sensitivity (in detecting prodromal AD in a QD group) and specificity (in differentiating AD from depression) of Cantab PAL was considerably better than that of all other frequently-used tests included in the study (including ADAS-cog and Wechsler Logical Memory Delayed Passage Recall).

The accumulating evidence demonstrates the sensitivity and specificity of Cantab PAL as a tool for operationalizing the criteria for objective memory impairment in mild cognitive impairment (MCI).

2 INDICATION(S) AND INTENDED USE

The application is designed to detect episodic memory impairments in patients aged 50 to 90 years who may be experiencing MCI or dementia (Table 1). Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression (Geriatric Depression Screening Questionnaire [GDS]), and problems with performing regular activities of daily living (Activities of Daily Life Questionnaire [ADL]). Additional information on questionnaires is provided in the Device Description document, **Section 11** of this submission.

Table 1. Indications for Use

Indications for Use	The device is intended to be used to assess memory in patients aged 50 to 90 years.
Contraindications	Patients with severe visual impairment Patients outside the indicated age range

The application provides test results that are interpretive, however, Cantab Mobile is not a diagnostic test. The output provided by the device is not diagnostic. A diagnosis can only be made by a qualified physician using consensus diagnostic criteria. The option to test or not to test is a decision that rests with the medical professional.

2.1 Instructions for Use

The Instructions for Use (IFU) is included as a separate document in Section 13 of this submission. Please see **NMI-013** for the full Instructions for Use for Cantab Mobile.

3 DEVICE DESCRIPTION

A full Device Description is included in a separate document in **Section 11** of this submission.

3.1 Summary

Cantab Mobile is software to be loaded and run on Apple iPad hardware and operating system. The software is intended to be administered by a healthcare professional to test the cognitive function of a patient. The Cantab Mobile memory test is based on the Cantab PAL test, which requires patients to learn and remember abstract visual patterns associated with various locations on a touch-sensitive computer screen. Two optional questionnaires are included to assess a patient's mood and ability to perform daily living activities. At the conclusion of the test, a 'thank you' screen is displayed with no information on test outcome. The healthcare professional will then be able to read or export a report, which summarizes the memory test results and also displays information on the patient's responses in the questionnaires, if these have been administered.

Cantab Mobile has been classified as a Class IIa Medical Device in accordance with:

- MEDDEV 2.1/6 – January 2012
- 93/42/EEC on Medical Devices, Classification Criteria, Annex IX, Rule 10.

4 VERIFICATION, VALIDATION AND TRACEABILITY

Software development is carried out under a controlled Software Development Life Cycle within a Quality Management System. A summary of the current version of these procedures in relation to IEC 62304:2006 for Class A software systems is provided in **QA-IEC62304Analysis.** See the Software section of this submission (Section 16).

Version 1.3 is the current version of the application. The history of prior application changes and verification is reflected in the table below.

Table 2. Description of Verification and Validation Activities

(b)(4)

In addition to the traceability of verification records and risk control activities provided in the above documents, traceability between requirements, functional design and software testing specifications is summarized in **NMI-018.**

Functional testing is conducted against controlled software versions using a defined test specification, which documents the criteria required for each test case to pass; the pass/fail outcome for each case is recorded in records of testing for the software version.

A revision history log of external software releases with version identification is maintained under the control of the software configuration management system.

5 SUBSTANTIAL EQUIVALENCE

5.1 Predicate Device

Cantab Mobile is substantially equivalent to DANA (manufactured by AnthroTronix; K141865). Cantab Mobile and DANA are both categorized as Attention Task Performance Recorders. The tests use different mobile devices; Cantab Mobile uses an Apple iPad and DANA uses a smartphone or tablet with the Android operating system. Cantab Mobile and DANA are both used by healthcare professionals to measure aspects of patients' cognition. Cantab Mobile and DANA differ in the areas of cognition measures in that Cantab Mobile assesses visuospatial episodic memory, whereas the DANA software measures reaction time (speed and accuracy). Cantab Mobile and DANA are similar in terms of technological characteristics as both electronically record objective performance measurements when the patient responds to stimuli presented on the screen by touching the screen. Differences in the design and performance of Cantab Mobile and DANA do not affect either the safety or effectiveness of Cantab Mobile for its intended use.

Table 3 presents a summary of each device for comparison. A complete comparison table is provided in Appendix A.

Table 3. Device Comparison Summary (Proposed Device vs. Predicate Device)

Comparison Items	**CANTAB Mobile- Cambridge Cognition Ltd.**	**DANA – AnthroTronix** (Submitted September 18, 2014)
510(k) Number	Not Yet Assigned	K141865
Trade Name	Cantab Mobile	DANA
Common Name:	Mobile Based Task Performance Recorder	
Classification Name:	Recorder, Attention Task Performance	
Regulatory Class:	Unclassified	
Indications for Use	Cantab Mobile is intended to be used to assess memory in patients aged 50 to 90 years. Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living.	DANA provides clinicians with objective measurements of reaction time (speed and accuracy) to aid in the assessment of an individual's medical or psychological state. DANA also delivers and scores standardized psychological questionnaires.

6 CLINICAL EVALUATION

6.1 Introduction

(b) (4)

The following evidence was considered:

1. (b) (4)
2. (b)(4)

(b)(4)

6.2 Objectives

(b)(4)

(b)(4)

(b) (4)

7 RISKS TO HEALTH

7.1 Summary

Risk management for the device is handled under controlled procedures within a Quality Management System. These procedures are designed to meet applicable requirements of EN ISO 13485:2012 and EN ISO 14971:2012.

A tabular summary of the risk analysis and other document references are provided in **Section 11** of this submission.

7.2 Determination of Level of Concern

Cantab Mobile's level of concern is classified as minor based upon the parameters and recommendations outlined in FDA's *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (2005), with negative responses to all questions in Tables 1 and 2. Regarding question 3 in Table 2, the app is a screening device for use by a learned intermediary in conjunction with other investigations; its operation does not lead directly to diagnosis or choice of appropriate medical care.

8 OVERALL CONCLUSIONS

Cantab Mobile is an app that runs on an iPad. It detects episodic memory impairments, in patients aged 50 to 90 years, and includes optional mood and functional assessments which can help detect symptoms of depression and problems with performing regular activities of daily living. The Cantab tests have a 30-year history of use in a range of clinical populations, supported by over 1500 published papers. Cantab Mobile includes the Cantab PAL test, which has been developed as a way of assessing episodic memory without language barriers. A series of independent studies have demonstrated that PAL is sensitive in detecting the earliest signs of prodromal Alzheimer's disease, up to 32 months prior to clinical diagnosis, and that it is relatively insensitive to major unipolar depression. The accumulating evidence demonstrates the sensitivity and specificity of PAL as a tool for operationalizing the criteria for objective memory impairment in mild cognitive impairment (MCI).

Cantab Mobile is not a diagnostic test. The results for a patient's PAL memory test are presented to the healthcare professional as one of three traffic-light coded categories. In conjunction with other investigations, these provide information to assist the professional in their assessment of the patient.

Cantab Mobile is substantially equivalent to AnthroTronix's DANA software in that they share the intended use of providing clinicians with objective measurements of cognition. Both are mobile applications that electronically record objective performance measurements as the patient responds to stimuli presented on the screen by touching the screen. Differences in the design and performance of Cantab Mobile from DANA, the predicate device, do not affect either the safety or effectiveness of Cantab Mobile for its intended use.

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10 APPENDICES

Appendix A. Predicate Device Comparison (Cantab Mobile and DANA)

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	DANA - AnthroTronix
510(k) Number	Not Yet Assigned	K141865
Device Information: Trade Name	Cantab Mobile	DANA
Device Information: Common Name:	Mobile Based Task Performance Recorder	Mobile Based Task Performance Recorder
Device Information: Classification Name:	Recorder, Attention Task Performance	Recorder, Attention Task Performance
Device Information: Device Class:	Unclassified The device has the same intended use, indications for use, and relies on technology that does not raise new safety and effectiveness questions to DANA.	Unclassified http://www.accessdata.fda.gov/cdrh_docs/pdf14/k141814.pdf
Predicate Device:	DANA (K141865)	QbTest, Qbtech AB (K122149)
Type of Use	Prescription Use (Part 21 CRF 801 Subpart D	Prescription Use (Part 21 CFR 801 Subpart D)
Submission Date:	TBD	September 18, 2014
Submitter Information: Company:	Cambridge Cognition Limited. Tunbridge Court, Tunbridge Lane Bottisham Cambridgeshire, CB25 9TU UK	AnthroTronix, Inc. 8737 Colesville Road, Suite L203 Silver Spring, MD 20910 USA
Design and Intended Use	Cantab Mobile is a mobile application indicated to provide clinicians with objective measurements of visuospatial episodic memory and mood to aid in the assessment of an individual's medical or psychological state. Results should be interpreted only by qualified professionals. Cantab Mobile was developed on a mobile platform to improve the access and availability of assessments.	DANA is a mobile application indicated to provide clinicians with objective measurements of reaction time (speed and accuracy) and standardized health assessments to aid in the assessment of an individual's medical or psychological state. Results should be interpreted only by qualified professionals. DANA was developed on a mobile platform to improve the access and availability of assessments.

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	DANA - AnthroTronix
Target population	Patients aged 50 to 90 years with concerns about their memory. Results are automatically adjusted for age, gender, education.	A wide age range from high school students to older patients with dementia.
Anatomical site	The brain: cognitive function	The brain: cognitive function
Test duration	The test takes approximately 10 minutes to complete.	Spectrum of tests: 5-Minute Rapid; 15-Minute Brief; 45-Minute Standard.
Scoring and reports	Automatic scoring and instant reports	Automatic scoring and instant reports
Where used	Cantab Mobile is software used on a tablet, therefore it can be administered in any suitable setting, e.g. a clinic or home.	DANA is software on a tablet or smartphone, therefore it can be administered anywhere.
Energy used	Cantab Mobile software runs on an Apple iPad, which has the following features: ▪ built-in 25-watt-hour rechargeable lithium-polymer battery; ▪ charging via power adapter or USB to computer system; ▪ up to 10 hours of use when charged.	The DANA software runs on Android tablets and smartphones, containing a rechargeable battery, charged via power adapter or USB to computer system. The energy used is hardware-dependent.
Human factors	Any healthcare professional can administer the test. To ensure reliable results, the iPad should be placed on a stand and the assessment should be administered in a quiet room, without disturbance. The voiceover and questionnaire texts are provided in a choice of languages.	DANA software can be self-administered by patients or administered by a health aide.
To whom is the product marketed /target audience?	Healthcare Rehabilitation	Healthcare Education Pharmaceutical Rehabilitation Government
Materials	N/A	N/A
Biocompatibility	N/A	N/A
Compatibility with the environment and other devices	N/A	N/A
Sterility	Sterility status is not needed for this software-only device	Sterility status is not needed for this software-only device
Safety: electrical; mechanical; chemical;	These safety issues are not applicable to this software-only device.	These safety issues are not applicable to this software-only device.

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	DANA - AnthroTronix
thermal; radiation.		
To whom is the product marketed /target audience?	Healthcare Rehabilitation	Healthcare Education Pharmaceutical Rehabilitation Government
How the device differs from Predicate device	Cantab Mobile is similar to DANA in terms of technological characteristics, as both electronically record objective performance accuracy as the patient responds to stimuli presented on the screen by touching the screen. Cantab Mobile differs from DANA in that it provides an assessment of episodic memory, compared to DANA which assesses attention. Cantab Mobile also presents assessments of depression and activities of daily living, which are not included in DANA.	

11 REFERENCED DOCUMENTS

Traceability Matrix (NMI-018)

Change Control and Validation Report (CR-NMI-004)

Title: PALD Traceability Matrix									Page 1 of 1		

(b)(4) Test Data

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(b)

(b)

Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2004;17:42–48
DOI: 10.1159/000074081

Accepted: June 6, 2003
Published online: October 13, 2003

Detecting Dementia: Novel Neuropsychological Markers of Preclinical Alzheimer's Disease

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Key Words
Alzheimer's disease · Early detection · Neuropsychological assessment · Paired Associates Learning · Graded Naming Test

Abstract
The results of a previous study have suggested that impaired performance on one neuropsychological test, CANTAB Paired Associates Learning (PAL), may serve as a marker for preclinical Alzheimer's disease (AD). In a group of individuals with 'questionable dementia', the baseline PAL performance was found to correlate significantly with subsequent deterioration in global cognitive function over an 8-month period. The present paper reports diagnostic outcome data for the same individuals 32 months after the first assessment and evaluates the predictive diagnostic utility of baseline neuropsychological measures. Thirty-two months after joining the study, 11 of the 43 'questionable dementia' patients met the criteria for probable AD diagnosis ('converters') and 29 remained free from AD ('non-converters'). Logistic regression analysis revealed that two tests of memory, in combination, could be used to predict a later diagnosis of probable AD with a high level of accuracy [$\chi^2(3) = 47.054$, $p < 0.0001$]. As predicted, these tests are measures of visuospatial learning (CANTAB PAL) and, also, semantic memory (Graded Naming Test). These two tests in combination appear to be highly accurate in detecting cognitive dysfunction characteristic of preclinical AD. Using these tests, a simple algorithm is described for calculating, with 100% accuracy for this sample of 40 patients, the probability that an individual with mild memory impairments will go on to receive a diagnosis of probable AD.

Introduction

Current criteria for the diagnosis of probable Alzheimer's disease (AD) stipulate deterioration in 2 or more areas of cognition (including memory), of sufficient magnitude to interfere with work or social function [1]. Critically however, substantial neuropathological change may have occurred before clinically significant symptoms appear [2]. Thus, commencing treatment of AD at the time of clinical diagnosis (whether with anti-amyloid deposit

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agents, cholinergic drugs or putative disease-modifying agents) may be suboptimal or even ineffective because of the advanced stage of neurodegeneration at that time. The identification of cognitive tests that are sensitive to early pathological changes would facilitate the diagnosis of patients in a 'prodromal' state (i.e. those in whom the pathological process is present but whose symptoms are currently subclinical). Such early detection would serve to maximise the potential therapeutic benefit of treatment, enhance patient quality of life and, in so doing, reduce the burden on residential and nursing care services. Consequently, a very high therapeutic and economic premium is placed on the early detection and diagnosis of AD.

In attempting to identify neuropsychological tests that are sensitive to the cognitive markers of prodromal AD, it is critical to ensure that performance on such tests is not deleteriously affected by other neuropsychiatric complaints that may confuse diagnosis. Furthermore, in order to achieve maximum diagnostic sensitivity, it is important to establish that performance on such tests is necessarily subserved by brain areas directly implicated in AD neuropathogenesis. Failure to acknowledge these factors will limit the clinical utility of neuropsychological approaches to the early detection of AD [3].

The earliest pathological markers of AD, neurofibrillary tangles and neuropil threads, are first seen in the transentorhinal cortex, before neuropathology later spreads to the entorhinal cortex and hippocampus proper [4]. Converging evidence from lesion studies in humans [5] and experimental animals [6, 7] and functional neuro-imaging studies in normal volunteers [8, 9] suggests that these brain areas are necessarily involved in visuospatial associative learning. Accordingly, it is likely that a decline in the visuospatial associative learning ability may be a good candidate marker of early neuropathological abnormality.

Consistent with this hypothesis, previous studies have demonstrated that the performance of individuals with mild AD on a test of visuospatial associative learning [CANTAB Paired Associates Learning (PAL)] was impaired relative to both demographically matched healthy controls [10] and to individuals with a neuropsychiatric condition that is difficult to differentiate clinically from early AD (e.g. depression [11]). Furthermore, we have recently shown [11] that, in a group of individuals with 'questionable dementia', baseline PAL results revealed an apparent subgroup of patients who performed like AD patients. Performance on PAL was also found to correlate significantly with subsequent deterioration in global cognitive function over an 8-month period. This is consistent with the hypothesis that the PAL-impaired subgroup was suffering from prodromal AD.

The aim of the present analysis was to determine whether neuropsychological test scores could be used to accurately identify individuals who were in the preclinical phase of AD at the time of presentation to a memory clinic. The present paper reports diagnostic outcome data for individuals in the questionable-dementia group 32 months after first assessment and evaluates the prognostic utility of baseline neuropsychological measures.

Methods

All procedures were approved by the relevant local research ethics committees, and the study was conducted in accordance with the Declaration of Helsinki [12]. All subjects gave their written informed consent.

Subjects

Forty-three patients were invited to join the study following their referral and first consultation at a memory clinic. The sample comprised both individuals with subjective complaints of memory loss, yet showing normal performance on objective tests, as well as individuals showing objectively identifiable cognitive deficits that were restricted to memory. Performance on other tests of language and visuospatial function was within the normal range, and activities of daily life were preserved. Patient history was corroborated by a collateral source, and clinical dementia rating (based on a semi-structured interview) was 0.5 in all cases.

At baseline, all subjects were aged between 50 and 80 years (mean age = 64.83, SEM = 6.30). None of the participants were suffering from unipolar depression (DSM-IV) [13], nor did they meet criteria for probable AD (NINCDS-ADRDA) [1] or any other dementia. Participants were screened for the following exclusion criteria: extrapyramidal signs or hallucinations; vascular dementias; current cancer treatment (radiotherapy or chemotherapy); uncontrolled diabetes; serious head injury requiring surgical intervention. Patients having suffered cerebrovascular events (e.g. transient ischaemic attack or stroke) or epilepsy were excluded at the discretion of a senior neurologist (J.R.H.).

Neuropsychological and Diagnostic Procedures

Each subject participated in 4 periods of assessment at 8-monthly intervals after referral (baseline, 8, 16 and 24 months ± 4 weeks). Where possible, the subjects were tested at their own home. This report is based on the data from the baseline neuropsychological assessment and subsequent diagnostic outcome data.

Assessment comprised a neuropsychological battery consisting of 20 tests, administered in 2 or 3 sessions within 3 weeks of each other, usually lasting 2 h each. Appropriate counterbalancing was implemented in order to minimise practice and order effects. As a substantial proportion of patients presenting at a memory clinic may be suffering from depression, the results of tests of attention and executive function are excluded from the present analysis. These tests have previously been shown to be impaired in depression [11], limiting their utility as a differential diagnostic tool in a clinical setting.

Table 1. Demographic and neuropsychological performance data for converters and non-converters

	Ref.	Task description/key measures	Converters	Non-converters	p value
Measures of global function/subject characteristics					
Age, years			72.0 (8.94)	62.10 (8.05)	0.002
Gender (ratio M/F)			5:6	12:17	0.546
NART	14	Pronunciation of irregular words (predicted verbal IQ)	117.05 (7.56)	119.18 (6.84)	0.40
Alzheimer's Disease Assessment Scale, cognitive section	15	Assessment scale of cognitive symptoms (total errors/30)	16.81 (5.11)	8.55 (3.83)	<0.001
MMSE	16	Screening test for dementia (total score/30)	25.09 (1.76)	29.00 (1.22)	<0.001
Geriatric Depression Scale	17	Self-reported depression scale (depressive responses/30)	7.45 (5.89)	9.72 (5.40)	0.254
Tests of mnemonic function					
Recognition					
Warrington Short Recognition	18	2-choice recognition of visually presented words (e.g. lake, clock) or photographs of male faces (list of 25 for each); total correct (max. = 25)			
Memory Tests for:					
Words			19.36 (3.75)	23.55(2.90)	<0.001
Faces			19.36 (3.26)	22.89 (2.99)	<0.001
CANTAB pattern recognition	10	2-choice recognition of abstract patterns (2 lists of 12); percentage correct	64.77 (11.98)	85.92 (10.23)	<0.001
CANTAB spatial recognition	10	2-choice recognition of locations of white boxes on computer screen (4 lists of 5); percentage correct	70.91 (13.93)	78.10 (10.89)	0.09
Doors test from Doors and People tests	19	4-choice recognition of photographs of doors (2 lists of 12); total correct (max. = 24)	12.83 (3.12)	16.31 (3.10)	0.003
CANTAB delayed matching to sample	10	4-choice recognition of abstract patterns sharing colour or pattern with distractors (10 trials at each delay: simultaneous, 0, 4, 12 s); total correct at 12-second delay (max. = 10)	5.27 (1.49)	6.55 (1.97)	0.048
Cued and free recall					
CANTAB PAL	10	Learning of 1 (2 stages), 2 (2 stages), 3 (2 stages), 6 (1 stage) and 8 (1 stage) visual pattern-location pairings; 10 presentations available at each stage (see fig. 1); number of errors made at 6-pattern stage (score accommodates attrition as in [11])	31.00 (15.21)	6.62 (8.42)	<0.001
Wechsler Logical Memory Recall	20	Free recall of 2 story passages immediately and after 30 min delay (25 items per story); total items recalled at 30 min delay (max. = 50)	2.36 (4.30)	16.59 (7.89)	<0.001
Semantic naming					
GNT	21	Naming of graded-difficulty line drawings (e.g. kangaroo, centaur); total items named (max. = 30)	19.54 (2.84)	24.62 (3.09)	<0.001
New semantic battery naming test	22	Naming of line drawings from 8 semantic categories (e.g. vehicles – sledge, train; fruit – orange, cherry); total items named (max.= 64)	60.55 (2.38)	62.66 (1.74)	0.004
Category fluency	23	Spontaneous naming of items from 3 semantic categories: animals, fruit, household items; total items named in 180 s (60 s per category)	38.36 (7.95)	53.83 (11.89)	<0.001

Results are means, with standard deviations in parentheses. NART = National Adult Reading Test.

Neuropsychological tests included standard measures already in clinical practice and computerised tests from the CANTAB battery (www.camcog.com); see references in table 1 for a full description of the tests. Two key tests, CANTAB PAL and the Graded Naming Test (GNT), are shown in figure 1. Neuropsychological testing and a clinical diagnostic interview were administered independently by different individuals. Incident cases of probable AD were diagnosed according to NINCDS-ADRDA criteria [1] by a senior neurologist (J.R.H.) up to 32 months after baseline assessment. The results of the neuropsychological tests (other than the Mini-Mental State Examination, MMSE) were not used in the assignment of diagnostic category.

Analytical and Statistical Procedures

Measures chosen from each test were those deemed to load most heavily and specifically upon the psychological function that the test was being used to assess. Differences between group means were tested for statistical significance using one-way ANOVA or non-parametric Kruskal-Wallis ANOVA as appropriate. Untransformed scores are presented in table 1. In order to decrease skew and stabilise

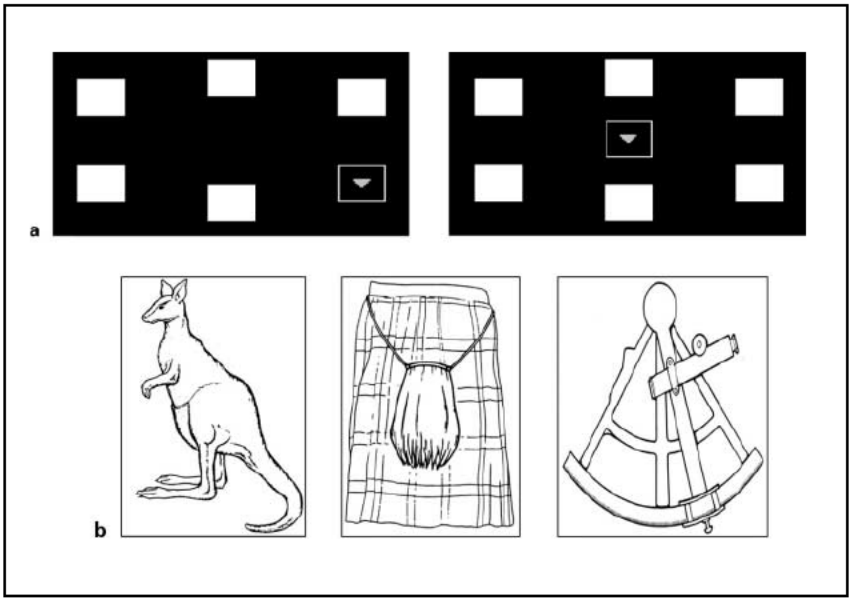

Fig. 1. a CANTAB PAL task. 1, 2, 3, 6 or 8 patterns are displayed sequentially in the available boxes (in the 8-pattern stage 2 more boxes are added). Each pattern is then presented in the centre of the display and the subject is required to touch the box in which the pattern was previously seen. If all the responses are correct, the test moves on to the next stage; an incorrect response results in all the patterns being redisplayed in their original locations, followed by another recall phase. The task terminates after 10 presentations and recall phases if all patterns have not been placed correctly. **b** GNT. Subjects are shown a series of 30 black-and-white drawings. Subjects are asked to name what each drawing represents, and their response is recorded. The figure shows 3 examples of naming stimuli: kangaroo, sporran, sextant.

variances some data were re-expressed prior to parametric analysis [for latencies ($x = \log_{10}(y)$; for proportions ($x = 2 \times \text{arcsine}\sqrt{y}$)]. Stepwise, feed-forward logistic regression analysis (using a likelihood ratio method) was conducted using SPSS version 10 [24].

Results

Diagnostic Outcome at 32 Months after Baseline

Thirty-two months after joining the study, 11 of the original 43 'questionable-dementia' patients met the criteria for probable AD diagnosis [1] ('converters') and 29 remained free from dementia ('non-converters'). This represents a conversion-to-AD rate of 26% over 2.7 years, comparable with conversion rates of questionable-dementia populations in previous studies [25]. Two patients were suspected to have Lewy body disease as they showed fluctuating cognitive impairment and parkinsonian-like symptoms (data from these subjects were excluded from analysis). One patient withdrew from the study prior to follow-up.

Baseline Demographic Characteristics of Converters and Non-Converters

There were no significant differences between the converters and non-converters in terms of gender ratio, affective status [17] (at entry to the study) nor estimated premorbid IQ [14] (table 1). The converters were significantly older than non-converters and, accordingly, age is included as a covariate in subsequent analyses. Converters also showed lower baseline MMSE [16] scores at entry than non-converters. However, it should be noted that the baseline MMSE scores of the converters ranged from 23 to 28, whereas those of non-converters ranged from 25 to 30. 32.5% of all questionable-dementia patients fell within a common range (i.e. 25–28), suggesting that the baseline MMSE would be of limited utility in identifying prodromal AD. Baseline MMSE scores are not included in predictive analyses as subsequent MMSE scores are used as a primary outcome measure.

Baseline Neuropsychological Test Performance of Converters and Non-Converters

The converter group performed significantly more poorly than the non-converter group on all tests of memory including: semantic naming ($p < 0.01$), cued and free recall ($p < 0.001$) and recognition ($p < 0.05$ for all measures except spatial recognition memory where $p = 0.09$).

The Utility of Neuropsychological Measures in Predicting Decline in Global Cognitive Function

A correlation matrix of baseline neuropsychological test scores and subsequent decline on MMSE over 24 months is shown in table 2. In accordance with the findings of Swainson et al. [11], the number of stages passed on CANTAB PAL was found to correlate significantly with the magnitude of global cognitive deterioration over

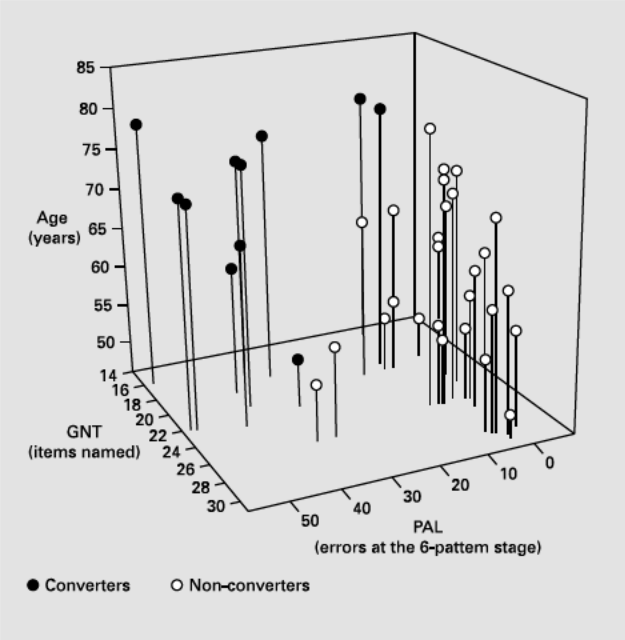

Fig. 2. Age, PAL and GNT performance of subjects with 'questionable dementia' at baseline. Black data points represent the scores of individuals who subsequently went on to receive a diagnosis of AD ('converters'). White points show the baseline scores of those subjects who remained non-demented at the 32-month follow up ('non-converters').

Table 2. Spearman's correlation coefficient of neuropsychological memory test performance at baseline and subsequent decline on MMSE over 2 years

Task	Correlation with global (MMSE) decline		
	r_s	p	
Global cognitive function			
ADAS-cog	–0.052	0.764	n.s.
Mnemonic tasks			
Warrington SRMT words	0.184	0.282	n.s.
Warrington SRMT faces	0.140	0.415	n.s.
Pattern recognition	0.137	0.427	n.s.
Spatial recognition	–0.235	0.168	n.s.
Doors recognition	0.268	0.114	n.s.
DMTS (correct 12 s delay)	0.105	0.541	n.s.
PAL (stages passed)	0.367	<0.05	*
PAL (6-pattern errors)	–0.174	0.310	n.s.
Logical memory (30 min recall)	0.173	0.314	n.s.
GNT	0.071	0.679	n.s.
Semantic naming	0.222	0.194	n.s.
Category fluency	0.248	0.145	n.s.

ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive section; SRMT = Short Recognition Memory Test; DMTS = delayed matching to sample.

the subsequent 2 years ($r_s = 0.37$, $p < 0.05$). The small but statistically significant relationships previously identified by Swainson et al. [11] between both PAL (6-pattern error score), and delayed matching-to-sample, and cognitive deterioration over an 8-month follow-up were not evident when cognitive deterioration was considered over a 24-month period.

The Utility of Baseline Neuropsychological Measures in Predicting Diagnostic Outcome at 32 Months

In order to determine which test, or combination of tests, could be used to construct a predictive diagnostic model, all baseline scores for tests of mnemonic function were entered into a multivariate logistic regression analysis (using a forward 'likelihood ratio' method), entering age as a covariate. Error at the 6-pattern stage of CANTAB PAL [12] was found to be the most predictive measure. This model (based on PAL and age alone) was highly significant [$\chi^2(2) = 34.417$, $p < 0.0001$] and correctly diagnosed 81.8% of the converters and 96.6% of the non-converters.

Adding a graded test of object naming (GNT) [21] to the model produces a 'perfect fit', i.e. this model perfectly distinguishes the converters and non-converters (of this sample) on the basis of their age, baseline PAL and GNT scores only. This enhanced model was also highly significant [$\chi^2(3) = 47.054$, $p < 0.0001$]. The PAL and GNT performance data for individual subjects are shown in figure 2.

Application of the PAL/GNT Model for the Detection of Prodromal AD in Memory-Impaired Patients

Using this model it is possible to construct a regression equation to estimate the odds (and probability) that an individual will go on to receive a diagnosis of probable AD. The regression equation is:

$$\log \text{odds AD}(x) = -115.742 + (4.254 \times \text{age}) + (6.517 \times \text{PAL}^{i}) - (13.87 \times \text{GNT}^{ii}),$$

where i = errors at the 6-pattern stage of CANTAB PAL and ii = total items named on the GNT(/30).

Exponentiating this term (e^x) gives the odds that the individual will develop AD. The predicted probability of

this individual going on to receive a diagnosis of probable AD within the next 32 months can then be calculated using the following equation:

probability of AD = $e^x/(1 + e^x)$.

Discussion

In an early report from this study [11], we showed that baseline CANTAB PAL performance correlated significantly with the degree of subsequent decline in global cognitive function in individuals with questionable dementia. With the addition of diagnostic outcome data, the present paper provides crucial confirmatory evidence that impaired performance on PAL may be used as an accurate marker of the prodrome to clinically diagnosed AD. Furthermore, with the addition of the GNT, outcome was predicted with a very high level of accuracy (100% for this sample of 40 patients).

Sensitivity of the PAL/GNT Model to AD Neuropathology

The predictive algorithm relating to findings from these two neuropsychological tests is consistent with what might be expected for functional deficits in terms of the known involvement of the medial temporal lobe and related areas in early AD. The transentorhinal region is a complex transitional area located between the entorhinal region proper and the adjacent temporal isocortex. It has been suggested [26] that damage to this site in early AD disrupts reciprocal connections with the hippocampal formation and that this disruption underlies deficits in episodic memory. By contrast, evidence suggests that deficits in semantic memory (such as object naming) may be attributable to abnormalities in the temporal neocortex [27–31]. Thus, we hypothesise that PAL and GNT are sensitive to early neurodegeneration in the transentorhinal region and the temporal neocortex proper, respectively. Accordingly, we suggest that by combining PAL and GNT, the model we have proposed is capable of maintaining diagnostic sensitivity whilst accommodating heterogeneity in the locus and spread of early AD pathology within medial temporal regions.

The validity of using PAL as a key marker for insidious AD pathology is further supported by the results of two other recent studies. Fowler et al. [32] found that impaired performance on the CANTAB PAL identified the onset of a progressive decline in memory, preceding both deterioration of performance on standard neuropsychological tasks and, ultimately, clinical diagnosis of AD. Although, in their study, the GNT was not administered, and considering that the participants were younger and drawn from a more clinically diverse population than those participating in our investigation, the similarity of the findings is very encouraging. Furthermore, De Jager et al. [33] have recently reported that CANTAB PAL (and to a lesser extent the GNT) could be used to detect the presence of memory deficits in elderly individuals whose performance on standard screening measures (MMSE [16] and CAMCOG [34]) was well within the normal range. These results suggest that the proposed predictive algorithm incorporating PAL and GNT may be sensitive to AD even prior to the onset of subjective memory complaints (indicating the potential utility of these two tests as community-based screening tools).

Specificity of PAL as a Marker for Early AD

Our early report [11] demonstrated that CANTAB PAL performance is spared in major unipolar depression [24]. Thus, in the clinic, impaired PAL performance is unlikely to be attributable to affective disturbance. The value of PAL in the differential diagnosis of neuropsychiatric conditions is further reinforced by the findings of a recent study by Lee et al. [35]. This recent study compared PAL performance of individuals with AD with that of individuals with frontotemporal dementia. In contrast to AD, frontotemporal dementia was shown to leave the key aspects of PAL performance largely unimpaired, suggesting that PAL may also be of use in the clinical differentiation of these disorders.

Considerations and Future Directions

It could be suggested that this study was limited by a restricted sample. However, by recruiting subjects from a well-defined population at a high risk of converting to probable AD, fewer participants were needed in order to detect an acceptable number of prodromal cases. Additionally, although this study did not involve the analysis of histopathological data, the NINCDS-ADRDA criteria for probable AD have previously been shown to accurately predict the neuropathological outcome [36].

It will be important in future studies to assess the extent to which the predictive utility of the PAL/GNT model performance is maintained in wider clinical and non-clinical populations. Additionally, we look forward to evaluating the extent to which novel techniques such as benzothiazole amyloid imaging [37] can usefully complement this neuropsychological approach, both in the context of early detection and treatment evaluation.

In summary, the results of the present investigation indicate that CANTAB PAL and the GNT are of major utility in the early and differential diagnosis of probable AD and are practical tools for use in the clinic.

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Early detection of isolated memory deficits in the elderly: the need for more sensitive neuropsychological tests

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ABSTRACT

Background. Early detection of cognitive decline in the elderly is important because this may precede progression to Alzheimer's disease. The aim of this study was to see whether sensitive neuropsychological tests could identify pre-clinical cognitive deficits and to characterize the cognitive profile of a subgroup with poor memory.

Methods. A neuropsychological test battery was administered to a community-dwelling sample of 155 elderly volunteers who were screened with CAMCOG at enrolment (mean age 74·7 years). The battery included tests of episodic memory, semantic and working memory, language and processing speed.

Results. Episodic memory test *z* scores below 1 S.D. from the cohort mean identified 25 subjects with 'non-robust' memory performance. This group was compared to the remaining 'robust memory' group with a General Linear Model controlling for age, IQ, education and gender. Test performance was significantly different in all tests for episodic and semantic memory, but not in tests for working memory, processing speed and language. CANTAB paired associates learning and spatial recognition tests identified the highest percentages of those in the 'non-robust memory' group. Processing speed partialled out the age effect on memory performance for the whole cohort, but the 'non-robust memory' group's performance was not associated with age or processing speed.

Conclusions. Sensitive neuropsychological tests can detect performance below the norm in elderly people whose performance on MMSE and CAMCOG tests is well within the normal range. Age-related decline in memory performance in a cohort of the elderly may be largely due to inclusion within the cohort of individuals with undetected pre-clinical Alzheimer's disease or isolated memory impairment.

INTRODUCTION

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Predicting Cognitive Decline in Healthy Older Adults

Celeste De Jager, Ph.D.
Andrew D. Blackwell, Ph.D.
Marc M. Budge, M.D.
Barbara J. Sahakian, Ph.D.

Objective: *Authors performed a neuropsychological determination of which individuals in a group of community-dwelling, healthy elderly volunteers would develop cognitive decline.* **Methods:** *A group of 155 volunteers reporting good memory and thinking participated in a prospective study over 4 years. Authors monitored cognitive functioning and incidence of Mild Cognitive Impairment (MCI)/Alzheimer disease (AD).* **Results:** *Baseline assessment revealed a subgroup of participants with deficits in associative learning and naming; subsequent cognitive decline was more precipitous in these individuals, who also showed higher relative risk of MCI/AD.* **Conclusion:** *Cognitive measures may be useful in community and clinical dementia screening and applicable for identifying enriched samples for trials of anti-dementia treatments.* (Am J Geriatr Psychiatry 2005; 13:735–740)

Received October 8, 2004; revised December 13, 2004; accepted March 30, 2005. From OPTIMA, University of Oxford, Dept. of Pharmacology, Oxford UK (CDJ), University of Cambridge, School of Clinical Medicine, Dept. of Psychiatry, Addenbrookes Hospital, Cambridge UK (ADB, BJS), and the Dept. of Geriatric Medicine, Australian National University Medical School, Canberra, Australia (MMB). Send correspondence and reprint requests to Barbara J. Sahakian, Ph.D., University of Cambridge, School of Clinical Medicine, Dept. of Psychiatry, Box 189, Addenbrookes Hospital, Cambridge CB2 2QQ, UK.

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Computerized delayed matching to sample and paired associate performance in the early detection of dementia

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Key words computerised neuropsychological testing; dementia of the Alzheimer type; discriminant function analysis.

Abstract This study examined the ability of two computerized neuropsychological tests, delayed matching to sample and paired associate learning, to detect early dementia. Three groups of subjects classified by NINCDS-ADRDA criteria and standard neuropsychological tests were studied: normal controls, patients believed to be in early stages of dementia of the Alzheimer type, and a group of questionable dementia subjects who reported memory loss but performed normally on standard measures of cognition. All subjects completed the two computerized tests. The early dementia group performed at a significantly lower level than the other two groups on all standard and computerized measures. A linear discriminant function analysis of the computerized tests classified 100% of the normal controls and 87.5% of the dementia patients into the same groups as standard testing. The majority of questionable dementia subjects were classified as nondemented. The concurrent validity and test-retest reliability of the computerised tests were also investigated. It is suggested that computerized tests are useful when screening for early dementia, and that longitudinal studies are required to evaluate the comparative reliability of the tests.

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Computerized neuropsychological tests in the early detection of dementia: Prospective findings

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(RECEIVED November 9, 1995; ACCEPTED April 25, 1996)

Abstract

This longitudinal study examines the sensitivity of 2 computerized neuropsychological tests, delayed matching to sample and paired associate learning, to early dementia of the Alzheimer type (DAT). Normal controls, patients in the early stages of DAT, and individuals with questionable dementia (QD) were studied. At 6 and 12 months after initial presentation, almost half of the QD group exhibited lower scores on the computerized subtests, maintaining their scores on standard testing. Over the same period NC subjects maintained their performance levels, while DAT patients continued to deteriorate. Linear discriminant function analyses of the computerized subtests at 6 and 12 months correctly classified 100% of the early DAT patients. Eighty-four and 79 percent of normal controls were correctly classified at 6 and 12 months respectively. Further development of these subtests for the detection of early dementia and the documentation of ongoing change in DAT is warranted. The findings are discussed in terms of the special sensitivity of these tests to the neuropathology of Alzheimer's Disease. (*JINS*, 1997, *3*, 139–146.)

Keywords: Computerized neuropsychological testing, Dementia of the Alzheimer type, Questionable dementia, Discriminant function analysis, Hippocampus

INTRODUCTION

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Paired associate performance in the early detection of DAT

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Abstract

Subjects underwent longitudinal neuropsychological assessment in order to retrospectively determine which measures of cognitive function best predicted later development of dementia of the Alzheimer type (DAT). Three groups of subjects were studied: normal controls, patients with early DAT, and questionable dementia subjects (QD). All subjects were assessed using a battery of standard neuropsychological measures and two subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB), paired associate learning and delayed matching to sample. A structured interview was also used to elicit a profile of the subject's daily functioning. Subjects were assessed every 6 months for 2 years. At the 6 month assessment, almost half of the QD group exhibited significant deterioration in scores on the computerized paired associate learning subtest, while maintaining their scores on standard measures. At the conclusion of the study, all of this QD subgroup fulfilled the NINCDS–ADRDA criteria for probable DAT pertaining to significant cognitive and functional deterioration. Performance on the CANTAB paired associate learning subtest identified the onset of progressive memory deterioration in a subgroup of QD subjects. In almost all cases this was well before significant deterioration was noted on standard neuropsychological measures. Paired associate learning performance may therefore be a valuable tool for the early, preclinical detection and assessment of DAT. (*JINS*, 2002, *8*, 58–71.)

Keywords: Alzheimer's disease, Questionable dementia, Neuropsychology, CANTAB, Hippocampus

INTRODUCTION

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SPECIAL ARTICLE

Monetary Costs of Dementia in the United States

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ABSTRACT

BACKGROUND

Dementia affects a large and growing number of older adults in the United States. The monetary costs attributable to dementia are likely to be similarly large and to continue to increase.

METHODS

In a subsample (856 persons) of the population in the Health and Retirement Study (HRS), a nationally representative longitudinal study of older adults, the diagnosis of dementia was determined with the use of a detailed in-home cognitive assessment that was 3 to 4 hours in duration and a review by an expert panel. We then imputed cognitive status to the full HRS sample (10,903 persons, 31,936 person-years) on the basis of measures of cognitive and functional status available for all HRS respondents, thereby identifying persons in the larger sample with a high probability of dementia. The market costs associated with care for persons with dementia were determined on the basis of self-reported out-of-pocket spending and the utilization of nursing home care; Medicare claims data were used to identify costs paid by Medicare. Hours of informal (unpaid) care were valued either as the cost of equivalent formal (paid) care or as the estimated wages forgone by informal caregivers.

RESULTS

The estimated prevalence of dementia among persons older than 70 years of age in the United States in 2010 was 14.7%. The yearly monetary cost per person that was attributable to dementia was either $56,290 (95% confidence interval [CI], $42,746 to $69,834) or $41,689 (95% CI, $31,017 to $52,362), depending on the method used to value informal care. These individual costs suggest that the total monetary cost of dementia in 2010 was between $157 billion and $215 billion. Medicare paid approximately $11 billion of this cost.

CONCLUSIONS

Dementia represents a substantial financial burden on society, one that is similar to the financial burden of heart disease and cancer. (Funded by the National Institute on Aging.)

From RAND, Santa Monica, CA (M.D.H., P.M., A.D., K.J.M.); the National Bureau of Economic Research, Cambridge, MA (M.D.H.); the Network for Studies on Pensions, Aging, and Retirement, Tilburg, the Netherlands (M.D.H.); the University of Essex, Essex, United Kingdom (A.D.); and the Division of General Medicine, Veterans Affairs Ann Arbor Center for Clinical Management Research, and the Institute for Healthcare Policy and Innovation, University of Michigan (K.M.L.) — both in Ann Arbor. Address reprint requests to Dr. Hurd at the Center for the Study of Aging, RAND, 1776 Main St., Santa Monica, CA 90401, or at mhurd@rand.org.

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Dementia, a chronic disease of aging characterized by progressive cognitive decline that interferes with independent functioning,[1] affects a large and growing number of older adults in the United States.[2,3] Citing the growing effect of dementia on patients, families, and the health care and long-term care systems, President Barack Obama signed the National Alzheimer's Project Act into law in January 2011. One goal of the law is to improve the ability of the federal government to track the monetary costs incurred by individuals and public programs, such as Medicare and Medicaid, that result from dementia.[4]

Accurately identifying the monetary costs attributable to dementia is challenging. First, persons with dementia are likely to have more coexisting chronic health problems than those without dementia, because they tend to be older and because certain diseases (e.g., stroke and depression) are more common in persons with dementia.[5] Thus, adjusting for the presence of these coexisting conditions is important in estimating the costs due to dementia alone, as opposed to the total costs for the population with dementia. Second, informal caregiving, the unpaid care provided by family and friends, in the form of assistance with activities of daily living (ADLs), is an important component of the support required by those with dementia,[6] yet it is unclear how to attribute a monetary cost to an informal caregiver's time.[7]

Given the aging of the population and the concomitant rise in the prevalence of dementia, the current uncertainty regarding the costs associated with dementia, and the recent focus of the federal government on developing a coordinated plan to address the growing effects of dementia, we sought to determine its monetary costs in the Health and Retirement Study (HRS).

Methods

Study Design

The HRS is a nationally representative longitudinal survey of persons 51 years of age or older that began in 1992.[8] Because the HRS lacks a direct measure of dementia status, a subset of 856 HRS respondents underwent a detailed in-home clinical assessment for dementia, 3 to 4 hours in duration, as part of the Aging, Demographics, and Memory Study (ADAMS), a nationally representative study of dementia in the United States.[2,9]

We used data on cognition and functional limitations from the HRS survey itself to estimate a three-category, ordered probit model[10] of the probability that an ADAMS respondent had dementia, had cognitive impairment but not dementia, or was aging normally. These data on cognition and functional limitations were available for all HRS respondents, not just the ADAMS respondents. For self-respondents, the HRS assesses cognitive function using a modified version of the Telephone Interview for Cognitive Status (TICS), a validated cognitive screening instrument designed for population-based studies.[11-14] For respondents represented by a proxy in the HRS, cognitive function was assessed with the use of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), a validated instrument consisting of 16 questions that address the respondent's memory and ability to function independently.[14,15] See the Supplementary Appendix, available with the full text of this article at NEJM.org, for details on these variables (Table S1 in the Supplementary Appendix) and for additional details on other data, methods, and results.

The HRS assesses whether respondents have limitations in the ability to perform six ADLs (eating, transferring [e.g., from a bed to a chair], toileting, dressing, bathing, and walking across a room) and five instrumental activities of daily living (IADLs; preparing meals, grocery shopping, making telephone calls, taking medications, and managing money).[16] We estimated the probability model over the ADAMS subsample using data from prior HRS interviews. To explain cognitive status, we used the variables of age, educational level, sex, ADL limitations, IADL limitations, and scores on TICS items (identification of the current date, backward counting from 20, subtracting by serial 7s, word naming, identification of the current U.S. president, immediate word recall, and delayed word recall) from the HRS interview immediately preceding the ADAMS assessment, and changes in ADL limitations, in IADL limitations, and in scores on TICS items from the two preceding HRS surveys. For HRS respondents represented by a proxy, a similar model was estimated with the use of the IQCODE.

To assess the within-sample fit of the model, we assigned a cognitive status of dementia if the fitted probability of dementia was greater than the fitted probability of normal aging or of cognitive impairment but not dementia. On the basis of this assignment, the within-sample fit was good: the specificity for dementia was 89.8% and the sensitivity was 77.9%. Overall, 85.7% of cases were correctly classified. We conducted a further validation by making out-of-sample predictions of dementia status for a subset of ADAMS respondents who were reassessed several years after the initial assessment. On follow-up, progression to dementia was found in 14.9% of respondents; our model predicted 13.9%. We then used this statistical model to estimate the probability of dementia for all HRS respondents older than 70 years of age in five HRS surveys (spanning the period from 2000 through 2008). See the Supplementary Appendix for further analyses of model performance.

MEASURES OF COST OF CARE

Out-of-Pocket Spending

The HRS asks respondents about health care utilization and coverage, and whether they have incurred any out-of-pocket health care expenses for the following services or items: nursing home stays, hospital stays, medical visits, outpatient surgery, home health care, special services (e.g., outpatient rehabilitation), prescription drugs, and dental services. Total annual out-of-pocket spending and spending according to type of care were computed for each year in the study period. All spending measures were converted to 2010 dollars with the use of the medical care Consumer Price Index.

Spending by Medicare

Information on Medicare spending is available for HRS respondents who have agreed to linkage of their Medicare claims records and who were enrolled in fee-for-service plans (approximately 70% percent of persons in our study population). These records have enrollment information and data on total annual payments by Medicare for durable-medical-equipment purchases, skilled nursing-facility care, hospice care, inpatient care, outpatient care, care provided by home health agencies, and care provided by noninstitutional providers of medical care.

Net Nursing Home Spending

We used the self-reported number of nights spent in a nursing home and nightly nursing home fees to estimate total nursing home spending, distinguishing fees according to state of residence and distinguishing between rates paid by Medicaid[17-23] and those paid by other third parties.[24] We reduced total nursing home spending by 8% because a portion of nursing home fees cover food and housing; such costs have to be paid whether or not someone has dementia and are therefore not attributable to dementia.

Formal and Informal Home Care

Information on the receipt of in-home assistance by persons with limitations in ADLs or IADLs was used to generate the average number of hours of care provided to persons at home. Caregiving is classified as "informal" when the caregiver is a relative or an unpaid nonrelative with no agency affiliation. All other care, whether obtained through an agency or provided by someone hired directly, is classified as "formal."[25] The methods used to calculate total hours of care have been described in earlier work[6] and are briefly summarized in the Supplementary Appendix.

To estimate the monetary value of formal care, we used 2010 average hourly rates charged by home health agencies in the respondent's state of residence.[24] We used two approaches to estimate the monetary cost of informal care. The "replacement cost" approach values care by using the cost of an equivalent service purchased in the market through a home health agency.[7] The "forgone wage" approach bases the valuation on the labor-market income forgone because of time spent on caregiving. For employed caregivers, we used the market wages reported by respondents in each HRS survey. Because most caregivers are not employed, we used average wages for persons with similar demographic characteristics (sex and, when reported, age and educational level). To account for the fact that many caregivers are elderly and out of the work force, we scaled down the imputed wages by multiplying by the rate of labor-force participation in the same demographic group, an approach that recognizes that many caregivers would not work even if they were not providing caregiving services. Our method estimates the loss of income and productive services to the market economy.

It does not measure the loss of well-being associated with alternative uses of caregiver time.

ESTIMATION OF THE COST ATTRIBUTABLE TO DEMENTIA

Persons with dementia have more coexisting conditions than those without dementia, conditions that by themselves lead to greater costs. To isolate the costs attributable to dementia, we estimated multivariate regression models that related a given cost component to the imputed probability of dementia, to coexisting conditions (stroke, diabetes, heart disease, hypertension, lung disease, cancer, psychiatric problems, and arthritis), and to demographic characteristics (age, household income, educational level, sex, and marital status). For details of these analyses, see Tables S6 through S10 in the Supplementary Appendix. We interpreted the estimated coefficient for the probability of dementia as the increase in costs associated with a change in the probability of dementia from 0 to 1.0, holding coexisting conditions and demographic characteristics constant.

We estimated two measures of the cost attributable to dementia. The first includes costs for care purchased in the market and is equal to the sum of the estimated increases in cost associated with dementia for out-of-pocket spending, Medicare spending, nursing home spending, and spending on in-home care. These estimates come from the multivariate models discussed above. The second measure adds in the monetary value of time spent by unpaid caregivers that is attributable to dementia, calculated as either the replacement cost or the cost of forgone wages.

RESULTS

PROBABILITY OF DEMENTIA

The average predicted probability of dementia, stratified according to personal and household characteristics, is shown in Table 1. Nonwhite race or ethnic group, female sex, single status, older age, lower educational level, and lower household income were associated with an increased likelihood of dementia ($P<0.001$ for all comparisons). Persons with one or more limitations in ADLs or IADLs were also more likely to have dementia, as were those who had a history of stroke or who had heart disease or a psychiatric condition ($P<0.001$ for all comparisons). However, persons who had a history of cancer were less likely to have dementia ($P<0.001$). The cost implications of these differences in demographic characteristics and coexisting conditions suggest the necessity of accounting for them in attributing costs to dementia.

ESTIMATED COST PER PERSON WITH DEMENTIA

Estimates of the yearly per-person costs attributable to dementia, both with and without adjustment for coexisting conditions and demographic characteristics, are shown in Table 2. Dementia was associated with a cost of $33,329 for care purchased in the market (95% confidence interval [CI], $24,223 to $42,434). That is, someone with a probability of dementia of 1.0 would be expected to incur $33,329 more in health care costs than someone whose probability of dementia was zero, when costs were aggregated over all payers. Adjustment for coexisting conditions and demographic characteristics reduced the cost estimate to $28,501 (95% CI, $20,881 to $36,122), a reduction of approximately 14%. The adjustments reduced attributable out-of-pocket spending and costs for formal home care and nursing home care by 3 to 18%, but the adjustments reduced attributable Medicare costs by 47%. On the basis of adjusted values, the most important attributable cost was for nursing home care (approximately $13,900), followed by out-of-pocket spending (approximately $6,200), formal home care (approximately $5,700), and Medicare (approximately $2,700).

The monetary value of informal home care attributable to dementia did not vary substantially when controlled for coexisting conditions and demographic characteristics. However, it varied by a factor of more than 2 when calculated on the basis of the replacement cost as compared with the cost of forgone wages.

After adjustment for coexisting conditions and demographic characteristics, the attributable yearly cost per person, including both the cost of care purchased in the marketplace and the cost of informal care, was $41,689 (95% CI, $31,017 to $52,362) when the valuation of forgone wages was used and $56,290 (95% CI, $42,746 to $69,834) when the valuation of replacement cost was used. Calculating the value of informal home care in terms of forgone wages yielded an estimate of the cost of unpaid caregiving that was

31% of the total cost; calculating the value of informal home care in terms of the replacement cost yielded an estimate of 49%.

ESTIMATED TOTAL COSTS

Estimates of the total cost of dementia to the U.S. economy now and in the future are shown in Table 3. To estimate these costs, we combined the adjusted cost per person with dementia shown in Table 2 with prevalence rates from ADAMS and population projections from the U.S. Census. For 2010, this estimation yielded a prevalence of 14.7% in the population older than 70 years of age and an annual population cost of $109 billion for care purchased in the market, with a cost of $159 billion to $215 billion when the estimated monetary value of informal care was included. By 2040, assuming that prevalence rates and cost per person with dementia remain the same, our estimates suggest that these costs will more than double because of the aging of the population. Although the ability to pay these costs will be ameliorated somewhat by a growing population, they are still expected to increase by 79% when calculated per adult (with adults defined as persons 18 years of age or older).

Table 1. Probability of Dementia According to the Characteristics of the Study Population.*

Characteristic	Distribution	Probability of Dementia (95% CI)	P Value for Comparison with Reference Group
	percent		
Race or ethnic group†			
White	86.7	0.097 (0.093–0.101)	Reference group
Hispanic	4.4	0.168 (0.149–0.187)	<0.001
Other	8.9	0.184 (0.170–0.199)	<0.001
Sex			
Female	60.7	0.121 (0.116–0.127)	Reference group
Male	39.3	0.088 (0.082–0.093)	<0.001
Marital status			
Married	45.9	0.065 (0.061–0.069)	Reference group
Unmarried	54.1	0.145 (0.138–0.151)	<0.001
Age			
71–74 yr	23.3	0.028 (0.026–0.031)	Reference group
75–79 yr	31.7	0.049 (0.045–0.053)	<0.001
80–84 yr	24.1	0.130 (0.123–0.137)	<0.001
85–89 yr	14.2	0.203 (0.192–0.215)	<0.001
≥90 yr	6.7	0.385 (0.365–0.406)	<0.001
Educational level			
Less than high-school graduate	32.2	0.159 (0.151–0.167)	Reference group
High-school graduate	33.1	0.103 (0.096–0.110)	<0.001
Some college or more	34.7	0.066 (0.060–0.071)	<0.001
Household income			
<$15,000	28.3	0.183 (0.174–0.191)	Reference group
$15,000–$29,999	31.8	0.104 (0.098–0.110)	<0.001
$30,000–$44,999	17.4	0.069 (0.063–0.074)	<0.001
$45,000–$59,999	8.7	0.062 (0.054–0.070)	<0.001
$60,000–$74,999	4.6	0.049 (0.041–0.058)	<0.001
≥$75,000	9.3	0.041 (0.035–0.046)	<0.001

Table 1. **(Continued.)**

Characteristic	Distribution	Probability of Dementia (95% CI)	P Value for Comparison with Reference Group
	percent		
Limitations in ADLs or IADLs			
No	65.1	0.042 (0.040–0.044)	Reference group
Yes	34.9	0.231 (0.222–0.240)	<0.001
Coexisting conditions			
None	6.4	0.091 (0.079–0.103)	Reference group
Stroke	13.5	0.182 (0.169–0.195)	<0.001
Diabetes	19.1	0.106 (0.099–0.114)	0.602
Heart disease	35.9	0.118 (0.112–0.124)	<0.001
Hypertension	62.3	0.106 (0.102–0.111)	0.235
Lung disease	11.8	0.104 (0.093–0.114)	0.407
Cancer	19.7	0.088 (0.081–0.096)	<0.001
Psychiatric condition	14.6	0.187 (0.174–0.201)	<0.001
Arthritis	69.6	0.107 (0.103–0.112)	0.615

* Data are based on a total of 31,936 person-years. For each characteristic, such as sex and marital status, the probability of dementia was calculated from the regression of the predicted probability of dementia on indicator variables for the categories taken by that characteristic, such as "male" and "female" in the case of sex and "unmarried" and "married" in the case of marital status. P values reflect the null hypothesis that the probability of dementia is the same as that for the reference group. CI denotes confidence interval.
† Race or ethnic group was reported by respondents in the Health and Retirement Study.

DISCUSSION

We used nationally representative data to document comprehensively the incremental increase in costs attributable to dementia that arise from market transactions for goods and services as well as the costs of unpaid caregiving. We found that dementia leads to total annual societal costs of $41,000 to $56,000 per case, with a total cost of $159 billion to $215 billion nationwide in 2010. Our calculations suggest that the aging of the U.S. population will result in an increase of nearly 80% in total societal costs per adult by 2040.

The main component of the costs attributable to dementia is the cost for institutional and home-based long-term care rather than the costs of medical services — the sum of the costs for nursing home care and formal and informal home care represent 75 to 84% of attributable costs. Our estimate places dementia among the diseases that are the most costly to society. The cost for dementia care purchased in the marketplace ($109 billion) was similar to estimates of the direct health care expenditures for heart disease ($96 billion in 2008, or $102 billion in 2010 dollars) and significantly higher than the direct health care expenditures for cancer ($72 billion in 2008, or $77 billion in 2010 dollars).[26] These costs do not include the costs of informal care, which are likely to be larger for dementia than for heart disease or cancer.

Although the costs attributable to dementia reported here are large, they are considerably smaller than those reported by the Alzheimer's Association,[27] which has estimated that in 2010 the monetary costs alone were $172 billion (2010 dollars) as compared with our estimate of $109 billion. There are several reasons for this higher estimate. It is likely that the cost per case reported by the Alzheimer's Association is higher because it was estimated on the basis of a sample from a more severely impaired population (persons identified in the Medicare Current Beneficiary Survey as having dementia). The higher cost is also based on a significantly larger estimate of the prevalence of dementia.[27] The national prevalence of dementia used by the Alzheimer's Association is derived from a study of

Table 2. Yearly Cost per Person Attributed to Dementia, in 2010 Dollars.

Variable	Yearly Cost per Person (95% CI)	
	Unadjusted	Adjusted for Demographic Characteristics and Coexisting Conditions
	dollars	
Care purchased in marketplace		
Total out-of-pocket spending	6,838 (4,854–8,821)	6,194 (4,522–7,866)
Total Medicare spending	5,226 (3,086–7,365)	2,752 (1,116–4,389)
Net formal home care	6,888 (4,775–9,000)	5,678 (3,739–7,618)
Nursing home care (excluding payments by Medicare and out-of-pocket spending)	14,377 (10,016–18,739)	13,876 (9,769–17,983)
Total	33,329 (24,223–42,434)	28,501 (20,881–36,122)
Informal home care		
Caregiving time valued according to replacement cost	30,839 (23,578–38,099)	27,789 (21,112–34,466)
Caregiving time valued according to cost of forgone wages	14,591 (10,910–18,273)	13,188 (9,636–16,740)
Grand total		
Care purchased in marketplace plus caregiving time valued according to replacement cost	64,168 (48,406–79,928)	56,290 (42,746–69,834)
Care purchased in marketplace plus caregiving time valued according to cost of forgone wages	47,920 (35,433–60,406)	41,689 (31,017–52,362)

Table 3. Projected Total and Per-Person Annual Monetary Costs of Dementia in the United States, in 2010 Dollars.*

Cost and Year	Care Purchased in Marketplace	Total Cost According to Valuation of Cost of Informal Care	
		Replacement Cost (95% CI)	Cost of Forgone Wages (95% CI)
Total cost (billions of $)			
2010	109 (86–132)	215 (171–259)	159 (126–192)
2020	129 (102–156)	255 (204–306)	189 (150–228)
2030	183 (145–221)	361 (289–434)	267 (212–322)
2040	259 (204–314)	511 (408–615)	379 (300–457)
Total per-person cost ($)			
2010	464 (416–511)	915 (825–1006)	678 (610–746)
2020	498 (445–550)	983 (882–1083)	728 (652–804)
2030	640 (569–712)	1,264 (1,128–1,400)	936 (833–1,039)
2040	831 (733–929)	1,641 (1,455–1,826)	1,215 (1,074–1,356)

* Confidence intervals, estimated with the use of bootstrapping, account for the sampling error in estimates of the effect of dementia on spending and in the prevalence of dementia but treat population projections as nonrandom. Per-person costs are total population costs divided by the number of persons 18 years of age or older.

three Chicago neighborhoods.[28] The diagnostic criteria for dementia used in that study did not require the presence of a limitation in ADLs or IADLs (a criterion that was used in ADAMS), a factor that probably led to the substantially higher estimate of the prevalence of dementia in the Chicago study.[29] Finally, the cost estimate from the Alzheimer's Association was not adjusted for the costs of coexisting conditions.[27]

Our analysis has several potential weaknesses.

First, as with all clinical assessments, the ADAMS diagnosis is subject to classification error, but a prior study that validated the ADAMS diagnostic methods with the use of neuropathological findings[30] and a meta-analysis of 27 studies of the incidence of dementia[31] suggest that the ADAMS approach achieves a diagnostic accuracy that is similar to that achieved by a reference standard for clinical evaluation. Second, we imputed dementia status to the entire HRS population rather than obtaining an actual clinical diagnosis for each respondent. Nonetheless, both the within-sample performance of the imputation model and the close correspondence between out-of-sample predictions based on our model and the follow-up assessments in ADAMS increase our confidence in the validity of our model. Furthermore, estimates of out-of-pocket spending based only on the ADAMS clinical assessments were similar to those reported here, but the ADAMS estimates had larger standard errors, reflecting its smaller sample.[32] Third, self-reported costs of care may be subject to inaccuracies. Fourth, we were not able to include attributable costs paid by Medigap policies. However, a rough estimate indicates that these costs are small and would not materially change our conclusions. Fifth, the costs of informal care are a major contributor to costs — yet attribution is difficult. For this reason, we presented a range of estimates. Sixth, regarding our cost forecasts, we assumed that the real cost per case of dementia will remain constant. Although the costs of health care services have increased faster than the rate of inflation, the majority of costs attributable to dementia are related to the informal and formal care provided to address limitations in ADLs and IADLs, and much of that care is provided by low-wage workers. Wages in the lower part of the wage distribution have been stable or have even decreased in real terms, so we believe our assumption is reasonable. Finally, we could not conduct a detailed assessment of attributable costs according to payer because we lacked a linkage to Medicaid records. From the perspective of public policy, such information would be valuable.

The views expressed are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. government.

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Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

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Abstract

Currently available evidence strongly supports the position that the initiating event in Alzheimer's disease (AD) is related to abnormal processing of β-amyloid (Aβ) peptide, ultimately leading to formation of Aβ plaques in the brain. This process occurs while individuals are still cognitively normal. Biomarkers of brain β-amyloidosis are reductions in CSF $A\beta_{42}$ and increased amyloid PET tracer retention. After a lag period, which varies from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes. Biomarkers of neuronal injury and neurodegeneration are increased CSF tau and structural MRI measures of cerebral atrophy. Neurodegeneration is accompanied by synaptic dysfunction, which is indicated by decreased fluorodeoxyglucose uptake on PET. We propose a model that relates disease stage to AD biomarkers in which Aβ biomarkers become abnormal first, before neurodegenerative biomarkers and cognitive symptoms, and neurodegenerative biomarkers become abnormal later, and correlate with clinical symptom severity.

Introduction

As recently as 2 to 3 decades ago, a compartmentalised model of Alzheimer's disease (AD) was widely accepted. The view at that time was that people either had AD pathological changes, in which case they had dementia, or they did not have such changes and were cognitively

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Conflicts of interest
CRJ is an investigator in clinical trials sponsored by Pfizer and Baxter, and consults for Elan and Lilly. DSK has served on a data and safety monitoring board for Lilly, has been a consultant for GlaxoSmithKline, and receives grant funding for clinical trials by Baxter, Elan, and Forest. WJJ has consulted for Genentech, Synarc, Elan Pharmaceuticals, Ceregene, Schering Plough, Merck & Co, and Lilly. LMS has consulted for Pfizer. PSA has consulted for Elan, Wyeth, Eisai, Neurochem, Schering-Plough, Bristol-Myers-Squibb, Lilly, Neurophase, Merck, Roche, Amgen, Genentech, Abbott, Pfizer, Novartis, and Medivation, has stock options with Medivation and Neurophase, and has received grant support from Pfizer, Baxter, and Neuro-Hitech. MWW has been on the scientific advisory boards for the Alzheimer's Study Group, Bayer Schering Pharma, Lilly, CoMentis, Neurochem, Eisai, Avid, Aegis, Genentech, Allergan, Bristol-Myers Squibb, Forest, Pfizer, McKinsey, Mitsubishi, and Novartis, has received travel funding from Nestlé, honoraria from BOLT International, commercial research support from Merck and Avid, and has stock options in Synarc and Elan. RCP has been a chair, member of the safety monitoring committee, and consultant for Elan, has chaired a data monitoring committee for Wyeth, and has been a consultant for GE Healthcare. JQT has received lecture honoraria from Wyeth, Pfizer, and Takeda.

normal. In the meantime, a revised view of the disease has been developed, in which both AD pathological processes and clinical decline occur gradually, with dementia representing the end stage of many years of accumulation of these pathological changes. An additional feature of the current view of AD is that these changes begin to develop decades before the earliest clinical symptoms occur.

Biomarkers, both chemical and imaging, are indicators of specific changes that characterise AD in vivo. Evidence suggests that these AD biomarkers do not reach abnormal levels or peak simultaneously but do so in an ordered manner. Measurement of these biomarkers in longitudinal observational studies is now commonplace, enabling investigators to establish the correct ordering of the relevant biomarkers and their relationships to clinical symptoms.

For biomarkers of AD to be used effectively for disease staging, the time-dependent ordering of biomarkers must be thoroughly understood. This is particularly true since the introduction of clinical trials of disease-modifying therapies in which disease biomarkers play an increasingly important part both as outcome measures and as inclusion criteria. We will review the five most well validated AD biomarkers. We then propose a hypothetical model of the time-dependent ordering of onset and maxima of these biomarkers. The purpose of this paper is to offer this model as a conceptual construct within which research studies from different disciplines can relate to one another through a common framework. The model suggests a series of testable hypotheses from which a clearer picture of the time-dependent trajectories of AD biomarkers relative to clinical disease stage and to each other can be derived.

AD clinical features and pathological changes

Dementia is the clinically observable result of the cumulative burden of multiple pathological insults in the brain. Most elderly patients with dementia have multiple pathological changes underlying their dementia; however, the most common pathological substrate is AD.[1,2]

The clinical disease stages of AD have been divided into three phases. First is a pre-symptomatic phase in which individuals are cognitively normal but some have AD pathological changes. To some extent, labelling these individuals as having pre-symptomatic AD is a hypothesis rather than a statement of fact, because some of these individuals will die without ever expressing clinical symptoms.[3–5] The hypothetical assumption is that an asymptomatic individual with pathological changes that are indicative of AD would ultimately have become symptomatic if he or she lived long enough. Second is a prodromal phase of AD, commonly referred to as mild cognitive impairment (MCI),[6] which is characterised by the onset of the earliest cognitive symptoms (typically deficits in episodic memory) that do not meet the criteria for dementia. The severity of cognitive impairment in the MCI phase of AD varies from the earliest appearance of memory dysfunction to more widespread dysfunction in other cognitive domains. The final phase in the evolution of AD is dementia, defined as impairments in multiple domains that are severe enough to produce loss of function.

Recent recommendations have suggested redefining research criteria for AD by labelling individuals with memory impairment plus accompanying biomarker evidence of AD as having early AD.[7] These investigators propose eliminating the distinction between pre-dementia (ie, MCI) and dementia, but this is not uniformly accepted because the label “dementia” serves a practical role in clinical practice. A clinical diagnosis of dementia is a clear indication to both the patient and family that the patient has a disorder that precludes independent living and has a decidedly worse prognosis than do milder forms of cognitive impairment, and implies that he or she is on an inevitable course toward complete loss of independence.

The concept of using biomarkers for early diagnostic purposes has a long history, with many studies showing that AD biomarkers can be used to predict conversion from MCI to AD. These

prediction studies show that individuals destined to develop AD can be identified earlier in the disease course by use of the MCI designation with the addition of imaging and CSF biomarkers to enhance diagnostic specificity.[8–13] However, at present, the clinical diagnosis of AD requires the presence of dementia.[14]

A widely accepted assumption is that AD begins with abnormal processing of amyloid precursor protein (APP), which then leads to excess production or reduced clearance of β-amyloid (Aβ) in the cortex.[15] All known forms of autosomal-dominant AD involve genes that either encode APP itself, or encode protease subunits (PS1 and PS2) that are involved in the cleavage of Aβ from APP to generate amyloidogenic Aβ peptides. By unknown mechanisms, but possibly as a result of the toxic effects of Aβ oligomers,16 one or more forms of Aβ leads to a cascade characterised by abnormal tau aggregation, synaptic dysfunction, cell death, and brain shrinkage.17

The abnormal protein deposits that characterise AD pathologically are well known: Aβ plaques and neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau. Neurodegeneration is as important as these hallmark pathological lesions of AD, and manifests as atrophy, neuron loss, and gliosis, which are routinely noted in research post-mortem examinations. Although the loss of synapses also is highly significant for the clinical manifestations of AD, this is difficult to assess without the use of labour-intensive morphometric methods, so it is not routinely measured in most AD research centres. Neurodegeneration and NFT deposition are both neuronal processes and occur in roughly the same topographic distribution. Aβ plaques are extracellular and occur in a different, but to some degree overlapping, topographic distribution from NFT and neurodegenerative pathological changes.

Clinical symptoms are more closely related to NFTs than to plaque formation.18,19 However, the most direct pathological substrate of clinical symptoms is neurodegeneration, and most specifically synapse loss.[20] Recent autopsy data have confirmed that gross cerebral atrophy (indicating the loss of synapses and neurons), and not Aβ or NFT burden, is the most proximate pathological substrate of cognitive impairment in AD.[5]

Panel: Imaging and CSF biomarker categories in Alzheimer's disease

Brain Aβ-plaque deposition

- CSF $A\beta_{1–42}$
- PET Aβ imaging

Neurodegeneration

- CSF tau
- Fluorodeoxyglucose-PET
- Structural MRI

Aβ=β-amyloid.

Biomarkers of AD

Biomarkers are variables (physiological, biochemical, anatomical) that can be measured in vivo and that indicate specific features of disease-related pathological changes. We have used the term "biomarker" to denote both imaging and biospecimen (ie, CSF) measures. We will focus on the five most widely studied biomarkers of AD pathology, based on the current literature: decreased CSF $A\beta_{42}$, increased CSF tau, decreased fluorodeoxyglucose uptake on PET (FDG-PET), PET amyloid imaging, and structural MRI measures of cerebral atrophy.

Each of these five biomarkers is well validated enough to be used in currently active therapeutic trials and large multisite observational studies. Other potential AD biomarkers are summarised elsewhere,[21,22] and are not discussed here. We briefly review the evidence supporting the position that each of these biomarkers is an in vivo indicator of a specific aspect of AD pathology (panel).

Biomarkers of Aβ-plaque deposition

Both CSF $A\beta_{42}$ and amyloid PET imaging are biomarkers of brain Aβ plaque deposition. Nearly all patients who have a clinical diagnosis of AD have positive amyloid imaging studies.[23–25] Excellent correspondence has been seen between Pittsburgh compound B (PiB) binding and fibrillar Aβ deposition in the brain (or cerebral vasculature) in most,[26,27] but not all,[28] patients who have undergone ante-mortem PiB-PET imaging and autopsy. PiB specifically binds to fibrillar Aβ, and not to soluble Aβ or to diffuse plaques.[26,27] Low concentrations of CSF $A\beta^{42}$ correlate with both the clinical diagnosis of AD and Aβ neuropathology at autopsy.[29–31] Nearly 100% concordance is present between abnormally low CSF $A\beta_{42}$ and positive PiB amyloid imaging findings in patients who have undergone both tests.[32–35] The evidence therefore strongly supports the notion that both amyloid imaging and low CSF $A\beta_{42}$ are valid biomarkers of brain Aβ-plaque load.

Biomarkers of neurodegeneration

CSF tau is an indicator of tau pathological changes and associated neuronal injury. Although phosphotau might be a more specific indicator of AD, concentrations of both phosphotau and total tau increase in AD.[36] Increased CSF tau is not specific for AD, but does correlate with clinical disease severity, with higher concentrations associated with greater cognitive impairment in individuals on the normal–MCI–AD cognitive spectrum.[37] In general, increases in CSF tau seem to indicate neuronal damage, and are seen in ischaemic and traumatic brain injury.[38,39] In AD, increased tau in the CSF is thought to occur as a direct result of tau accumulation in neurons, particularly axons; this disrupts neuronal activity and causes release into the extracellular space of cytoskeletal elements, including tau, which then appear in the CSF.[40,41] Increased CSF tau correlates with the presence of NFTs at autopsy.[42] Of note, for reasons that remain elusive, similar increases in CSF tau are not seen in pure tauopathies such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), despite the fact that the brains of patients with CBD often show far more tau accumulation than do the brains of patients with AD at autopsy.[43,44] This might suggest that extracellular Aβ plaques have an effect on the clearance of tau released from degenerating neurons in AD, that different species of pathological tau are involved in AD versus CBD and PSP, or that other factors render tau more readily diffusible and less degradable in AD versus CBD and PSP.[45]

FDG-PET is used to measure net brain metabolism, which, although including many neural and glial functions, largely indicates synaptic activity.[46,47] Brain glucose metabolism measured with FDG-PET is highly correlated with post-mortem measures of the synaptic structural protein synaptophysin.[48] In the context of AD, decreased FDG-PET uptake is an indicator of impaired synaptic function. FDG-PET studies in patients with AD show a specific topographic pattern of decreased glucose uptake in a lateral temporal-parietal and posterior cingulate, precuneus distribution.[49] Correction for cortical atrophy in patients with AD leaves metabolism still diminished.[50] Greater decreases in FDG uptake correlate with greater cognitive impairment along the continuum from normal cognitive status to MCI to AD dementia.[51] Combined imaging and autopsy studies show good correlation between the ante-mortem FDG-PET diagnosis of AD and post-mortem confirmation.[52] In cognitively normal elderly individuals, correlations are seen between decreased FDG-PET uptake and both low CSF Aβ and increased CSF tau.[53] Together, these data indicate that FDG-PET uptake is a valid indicator of the synaptic dysfunction that accompanies neurodegeneration in AD.

Structural MRI can provide measures of cerebral atrophy, which is caused by dendritic pruning and loss of synapses and neurons.[54] Volumetric or voxel-based measures of brain atrophy show a strong correlation between the severity of atrophy and the severity of cognitive impairment in patients along the continuum from normal cognitive status to AD dementia.[55] Thus, rates of neuronal and synaptic loss indicated by the progressive rate of brain atrophy correlate with rates of cognitive decline.[56] Atrophy on MRI is not specific for AD, but the degree of atrophy correlates well with Braak staging at autopsy.[57–59] Additionally, the topographic distribution of atrophy on MRI maps well onto Braak's staging of NFT pathology in patients who have undergone ante-mortem MRI and post-mortem AD staging.[60]

Temporal ordering of biomarker abnormalities

A crucial element of biomarker-based staging of AD is the notion of temporal ordering of different biomarkers. The model that we propose, which relates pathological stage to AD biomarkers, is based on a largely biphasic view of disease progression.[61,62] In this model, biomarkers of Aβ deposition become abnormal early, before neurodegeneration and clinical symptoms occur. Biomarkers of neuronal injury, dysfunction, and neurodegeneration become abnormal later in the disease. Cognitive symptoms are directly related to biomarkers of neurodegeneration rather than biomarkers of Aβ deposition. We examine evidence to support these time-dependent assumptions, beginning with evidence that biomarker abnormalities typically precede clinical symptoms.

Biomarker abnormalities precede clinical symptoms

Approximately 20–40% of cognitively normal elderly people have evidence of significant brain Aβ-plaque deposition, either from amyloid imaging or CSF $A\beta_{42}$ concentrations.[37,63–66] These data on Aβ imaging and CSF biomarkers are in agreement with autopsy studies that also show an AD pathological burden sufficient to meet criteria for a diagnosis of AD in roughly the same proportion of cognitively normal elderly individuals.[3–5] These data support the principle that the presence of Aβ-plaque deposition alone, even in substantial quantities, is not sufficient to produce dementia, and that abnormalities in biomarkers of Aβ deposition precede clinical/cognitive symptoms.[67–71] This principle is clearly illustrated by data from the individual in figure 1B who was cognitively normal with no evidence of atrophy on MRI, but had a highly abnormal PiB study. Calculated rates from serial PiB imaging studies indicate that Aβ-plaque accumulation in individuals destined to become demented might begin as much as two decades before the manifestation of clinical symptoms.[62] We note that both Aβ deposition and NFTs can be present in individuals with no symptoms. However, the presence of NFTs in asymptomatic individuals tends to be confined to the entorhinal cortex, Braak stage I–II, whereas NFTs in symptomatic individuals are far more widespread.[3–5,72] By contrast, Aβ-plaque deposition can be widespread in clinically asymptomatic individuals.

There is strong evidence that MRI, FDG-PET, and CSF tau biomarkers are already abnormal in patients who are in the MCI phase of AD.[37,51,73–75] Abnormalities in neurodegenerative AD biomarkers also precede the appearance of the first cognitive symptoms. Of the three neurodegenerative biomarkers, evidence that FDG-PET abnormalities precede any cognitive symptoms in individuals who later progress to AD is probably the strongest.[76,77] However, rates of atrophy on MRI do become abnormal in cognitively normal individuals who later progress to AD.[78–80] Thus, the available data strongly support the conclusion that abnormalities in both Aβ and neurodegenerative biomarkers precede clinical symptoms.

Aβ biomarker abnormalities precede neurodegenerative biomarker abnormalities

The rate of MRI atrophy on serial imaging studies is greatest in patients with a clinical diagnosis of AD, least in cognitively normal individuals, and intermediate in those with a clinical

diagnosis of MCI. By contrast, rates of change in PiB retention over time are just slightly greater than zero for all these three clinical groups, and do not differ by clinical group.[62] Thus, in patients who are rapidly declining clinically (ie, patients with AD) MRI rates map well onto simultaneous cognitive deterioration, whereas rates of change in PiB do not.[62,81] Similarly, CSF Aβ does not change significantly over time in patients with AD. Rates of brain atrophy correlate well with pathological indices of NFTs and other neurodegenerative changes, but do not correlate with severity of Aβ deposition at autopsy.82 Cognitively normal individuals with positive Aβ imaging studies might have normal structural MRI studies, implying that a substantial Aβ load can accumulate with no immediate effect on gross brain structure or cognition (figure 1).[83] In a modelling study inferring cause and effect, Mormino and colleagues[84] found that the direct substrate of memory impairment was hippocampal atrophy on MRI, and not Aβ deposition as measured by PiB imaging. Frisoni and colleagues[85] also placed amyloid deposition before MRI changes in the sequence of events. These findings support the conclusion that an abnormality in biomarkers of Aβ-plaque deposition is an early event that nears a plateau before the appearance of both atrophy on MRI and cognitive symptoms, and remains relatively static thereafter. By contrast, abnormalities in neurodegenerative biomarkers on MRI accelerate as symptoms appear, and then parallel cognitive decline.

Neurodegenerative biomarkers are temporally ordered

Available evidence suggests that FDG-PET changes might precede MRI changes.[77,86,87] Up to this point, we have discussed the temporal ordering of AD biomarkers from the perspective of which biomarker becomes abnormal earlier during the progression of AD. However, the order in which the dynamic range of biomarkers approaches its maximum is also relevant to the discussion of biomarker ordering. MRI and CSF tau correlate well with cognition if individuals who span the entire cognitive spectrum (controls, MCI, and AD) are combined. However, among patients with MCI or AD alone, correlations with measures of general cognition are strong with structural MRI, but are not significant with CSF tau.[88] These data are consistent with studies indicating that CSF tau does not change appreciably over time in cognitively impaired patients.[89,90] Furthermore, although both MRI and CSF tau are predictive of future conversion from MCI to AD, the predictive power of structural MRI is greater.91 These findings imply that the correlations between cognition and CSF tau weaken as patients progress into the mid and late stages of the clinical AD spectrum. Conversely, structural MRI measures of atrophy retain a highly significant correlation with observed clinical impairment in both the MCI and dementia phases of AD. Moreover, rates of atrophy on MRI are significantly greater in patients with AD than in cognitively normal elderly individuals.[92] This body of literature implies that MRI atrophy is a later event in AD progression, preceded by abnormalities in CSF tau and FDG-PET, and that MRI retains a closer correlation with cognitive symptoms later in disease progression than does CSF tau.

Use of biomarkers to stage AD in vivo

Autopsy studies have been, and will continue to be, essential in uncovering the biological basis of the clinical symptoms in AD. However, by definition, autopsy studies are unable to provide clinical–histological correlations during life, when pathological changes actually occur, resulting in an inability to isolate relationships between time-dependent histological changes and clinical/cognitive consequences. This point underlies the value of using biomarkers in the staging of disease.

On the basis of the evidence presented above, we propose the use of specific AD biomarkers for disease staging in vivo. The disease model and biomarker staging are shown in figure 2, which embodies the following set of principles. First, the biomarkers become abnormal in a temporally ordered manner as the disease progresses. Second, Aβ-plaque biomarkers are

dynamic early in the disease, before the appearance of clinical symptoms, and have largely reached a plateau by the time clinical symptoms appear. Third, biomarkers of neuronal injury, dysfunction, and degeneration are dynamic later in the disease and correlate with clinical symptom severity. Fourth, MRI is the last biomarker to become abnormal; however, MRI retains a closer relationship with cognitive performance later into the disease than other biomarkers. [88,91] Fifth, none of the biomarkers is static; rates of change in each biomarker change over time and follow a non-linear time course, which we hypothesise to be sigmoid shaped. Non-linearity has been clearly shown in MRI studies, in which atrophy rates accelerate as patients approach clinical dementia.[93,94] A sigmoid shape as a function of time implies that the maximum effect of each biomarker varies over the course of disease progression.[95] Comprehensive biomarker-based staging of disease in an individual at a given point in time should be possible from measures of the magnitude and slope (ie, rate of change) of several different biomarkers (figure 3). Sixth, anatomical information from imaging biomarkers provides crucial disease-staging information. Similar to NFT accumulation, cerebral atrophy, for example, begins in medial temporal limbic areas and spreads from there to adjacent limbic and paralimbic areas and later to the isocortical association cortex.[96] Therefore, at a given timepoint, different brain areas will be at different stages. In any given area of an individual's brain there might be an amyloid phase, a neuronal dysfunction phase, etc, and this will occur in an anatomical order (figure 4). This implies an advantage for imaging biomarkers over fluid biomarkers, because imaging can resolve the different phases of the disease both temporally and anatomically. Finally, a feature of this biomarker model of AD is the presence of a lag phase of unknown duration between Aβ-plaque formation and the neurodegenerative cascade. Between-patient variation in the lag period between Aβ deposition and the neurodegenerative cascade is probably an indication of differences in Aβ processing, in the effects of abnormal Aβ processing on neuronal injury, and differences in brain resilience or cognitive reserve.[97] Other pathological changes, particularly cerebrovascular, α-synuclein, and TAR DNA-binding protein 43 proteinopathy mechanisms, also contribute significantly to between-individual variations in clinical disease expression.[98]

Clinical trials

Our proposed model has implications for clinical trials. For example, it is rational to select patients for inclusion in trials of anti-Aβ therapies on the basis of biomarker evidence of the presence of Aβ in the brain by use of either amyloid PET imaging or CSF $A\beta_{42}$. Although biomarkers of neurodegeneration correlate with clinical and pathological severity, they are not specific for AD and thus should not take precedence over Aβ biomarkers as inclusion criteria for patients in anti-amyloid therapeutic trials (although an Aβ biomarker might be combined with MRI volumetrics to provide an indication of disease stage). Conversely, change in Aβ load over time has little relation to change in cognition in natural history studies. In addition, evidence of therapeutic plaque removal in patients who already have dementia does not seem to correlate with a change in the trajectory of cognitive deterioration (at least, not in every case examined).[99] Measures of the neurodegenerative portion of the cascade (eg, CSF tau, FDG-PET, or structural MRI) should therefore be used in therapeutic trials as evidence of therapeutic modification of the neurodegenerative aspect of the AD pathological process. Therapeutic modification of the slopes of clinical outcome measures is a common outcome metric used in clinical trials. A consideration in the use of biomarkers as co-primary outcome measures is the fact that the slopes (rates of change over time) of different biomarkers vary over the course of the disease (figure 3). Ultimately, a combination of biomarkers might be needed in clinical trials to select appropriate participants and to follow disease progression.

Caveats

We have attempted to integrate the five most thoroughly validated biomarkers of AD pathology into a model that is supported by currently available data. We have used a best-fit approach, realising that every published observation cannot neatly fit into our (or any other) single idealised model of disease progression. The proposed biomarker model represents a model of typical disease progression. We certainly do not preclude the existence of individual deviations from this generic model.

Although we have used the available evidence to support our model relating biomarkers to disease stage in AD, we recognise that some of the proposed relationships take the form of hypotheses rather than statements of fact. For example, although Aβ imaging and CSF Aβ are denoted as occurring simultaneously (figure 2, figure 3, and figure 5), it might be that one precedes or plateaus earlier than the other. The same logic applies to the timing relationships between FDG-PET and CSF tau. We have superimposed these curves in the current model not because there is good evidence to suggest that the curves should be identical, but because there is not good evidence at present to show that they are different. We also acknowledge that temporal ordering among the neurodegenerative biomarkers might ultimately differ from that in our proposed model.[100] For example, recent data from Fagan and colleagues[68] suggest that MRI atrophy might precede increases in CSF tau.

We recognise that well-validated biomarkers do not currently exist for some important features of the disease. This includes reliable chemical biomarkers of specific toxic oligomeric forms of soluble Aβ and imaging measures of soluble Aβ or diffuse plaques. We are therefore not in a position to include in our model important mechanistic features such as the role of toxic Aβ oligomeric species and the timing of their appearance. The absence of PET ligands that specifically measure the burden of NFTs and other tau abnormalities also constitutes a serious gap in our current armamentarium of imaging biomarkers. Another shortcoming is the absence of a widely accepted biomarker for microglial activation. PET imaging ligands and the magnetic resonance spectroscopy metabolite myo-inositol have been proposed as potential biomarkers of glial activation;[101,102] however, neither is widely used for this purpose at present. Thus, our biomarker model of disease is just that—a model of the stages of disease that can be assessed with currently validated biomarkers, and not a comprehensive model of all pathological processes in AD. In this context, we acknowledge that all biomarker information about disease is limited by the inevitable filter imposed by detection sensitivity and measurement precision. Clearly, an in vivo measure is unlikely to be as sensitive to the underlying pathology as a detailed autopsy examination would be.

An observation that does not fit our model is that of Braak and Braak,72 who concluded that stage I–II (entorhinal) NFT changes precede isocortical Aβ changes, leading to the conclusion that NFT accumulation is the initiating event in AD.[103] However, the following observations contradict this conclusion: (1) the genetics data in early-onset AD, which implicate disordered Aβ metabolism as the initiating event; (2) the fact that the final pathological picture is identical between late-onset and early-onset AD cases; and (3) the fact that the major genetic risk factor of late-onset AD (*APOE* ε4) is implicated in disordered trafficking of Aβ peptide.[104]

Observations that will need to be incorporated into future revisions of this model relate to evidence of disordered glucose uptake in cognitively normal young and middle-aged *APOE* ε4 carriers up to decades before disease-related clinical symptoms would be expected to appear.[105,106] No consensus exists on the interpretation of these observations at this point. These findings could be neurodevelopmental in origin or early indicators of AD.[107,108]

Conclusions

Our main objective was to provide a framework for hypothesis testing that relates temporal changes in AD biomarkers to clinical disease stage and to each other. The temporal relationships among the biomarkers and with clinical disease stage constitute an array of testable hypotheses. For example, carriers of *APOE* ε4 have an earlier age of onset of dementia than non-carriers,[109] and we hypothesise that *APOE* ε4 carriers will have a leftward (earlier in time) shift of both the Aβ-plaque and neurodegenerative biomarker cascades relative to non-carriers (figure 5).[110] We also hypothesise that modifiers of the relationship between Aβ pathological changes and their downstream effect on cognition might alter the lag time between Aβ-plaque deposition and cognitive decline (figure 5). For example, the cognitive decline curve might shift closer to the Aβ curve (to the left) in individuals with comorbidities (eg, vascular disease), whereas the cognitive decline curve would shift away from the amyloid curve (to the right) in individuals with enhanced cognitive reserve.[97] Similarly, as yet undiscovered neuroprotective genes might shift the cognitive decline curve to the right, away from the amyloid curve, whereas genes that amplify the effect of Aβ dysmetabolism on the neurodegenerative cascade might shift the cognitive decline curve closer to the amyloid curve. For example, recent genome-wide association studies have identified new susceptibility loci involving *CR1*, *CLU*, and *PICALM* genes.111›112 Clusterin (apolipoprotein J) seems to regulate the toxicity and solubility of Aβ and might modify its clearance at the blood–brain barrier.111 CR1 might also modify Aβ clearance.112 PICALM might be related to AD through a role in altering synaptic vesicle cycling or APP endocytosis.111 Finally, we anticipate that other diagnostic modalities (eg, functional MRI connectivity)113–115 will be added to this biomarker staging model as they mature.

Search strategy and selection criteria

References for this paper were identified through searches of PubMed between 1984 and October, 2009, with combinations of the search terms “Alzheimer’s disease”, “dementia”, “MCI”, “imaging”, “PET”, “PiB”, “amyloid imaging”, “MRI”, and “biomarker”. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed.

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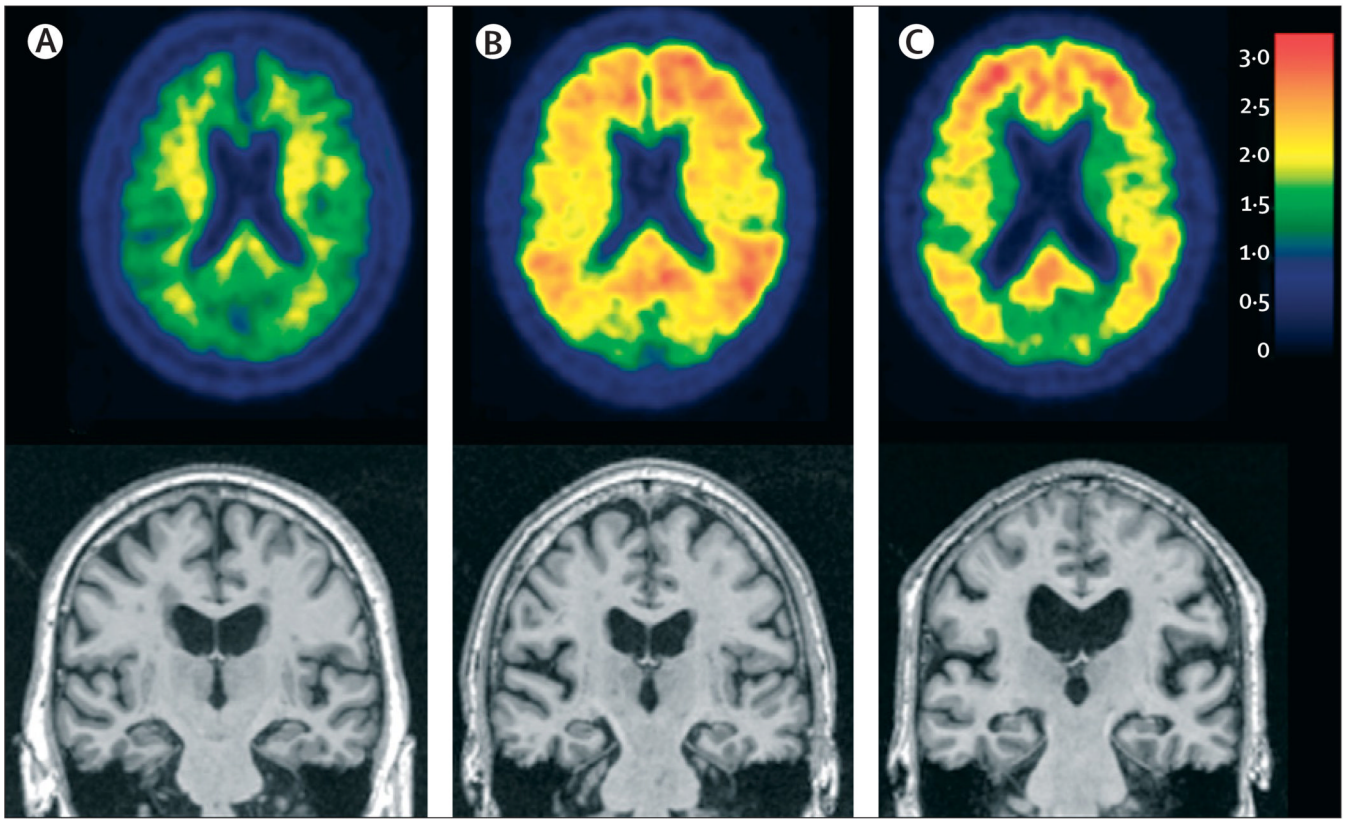

Figure 1. Illustration of biomarker staging of Alzheimer's disease

Three elderly individuals are placed in order from left to right by use of our proposed biomarker staging scheme. (A) A cognitively normal individual with no evidence of Aβ on PET amyloid imaging with PiB and no evidence of atrophy on MRI. (B) A cognitively normal individual who has no evidence of neurodegenerative atrophy on MRI, but has significant Aβ deposition on PET amyloid imaging. (B) An individual who has dementia and a clinical diagnosis of Alzheimer's disease, a positive PET amyloid imaging study, and neurodegenerative atrophy on MRI. Aβ=β-amyloid. PiB=Pittsburgh compound B.

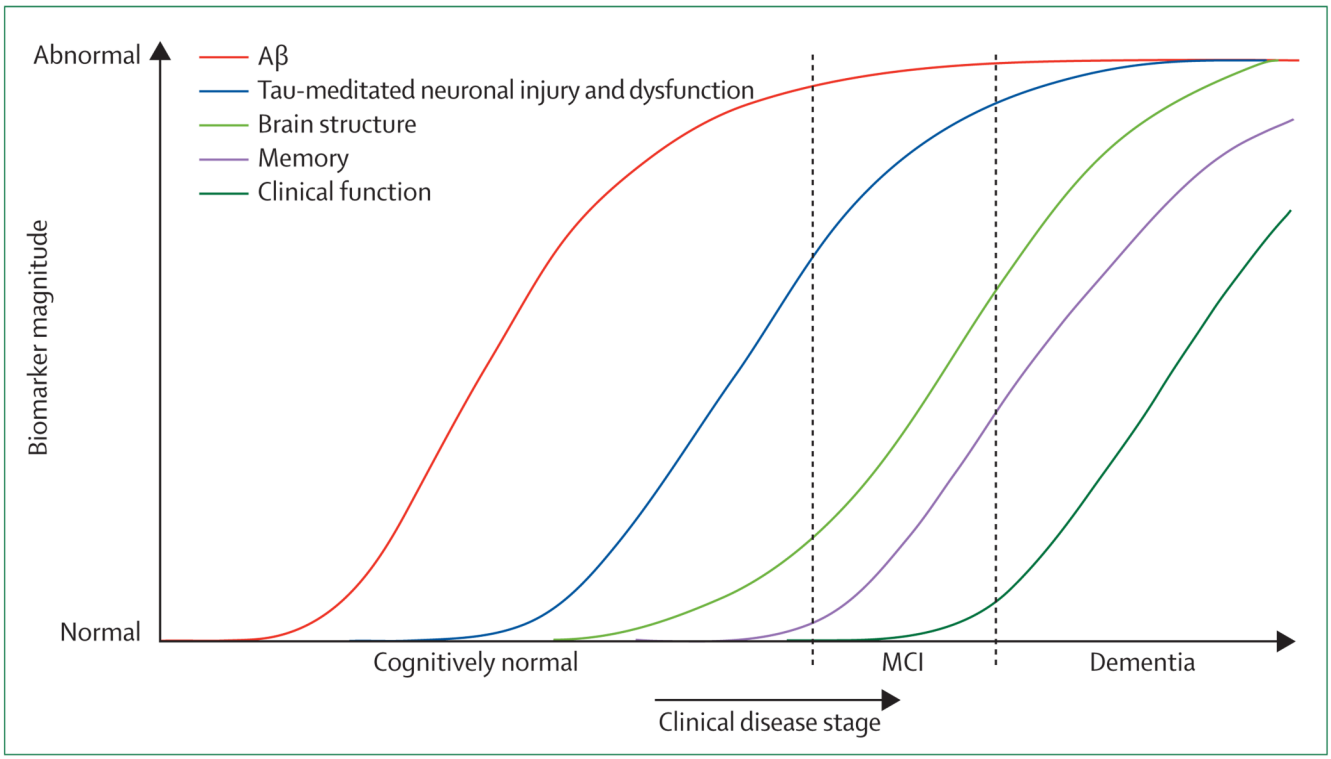

Figure 2. Dynamic biomarkers of the Alzheimer's pathological cascade

Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

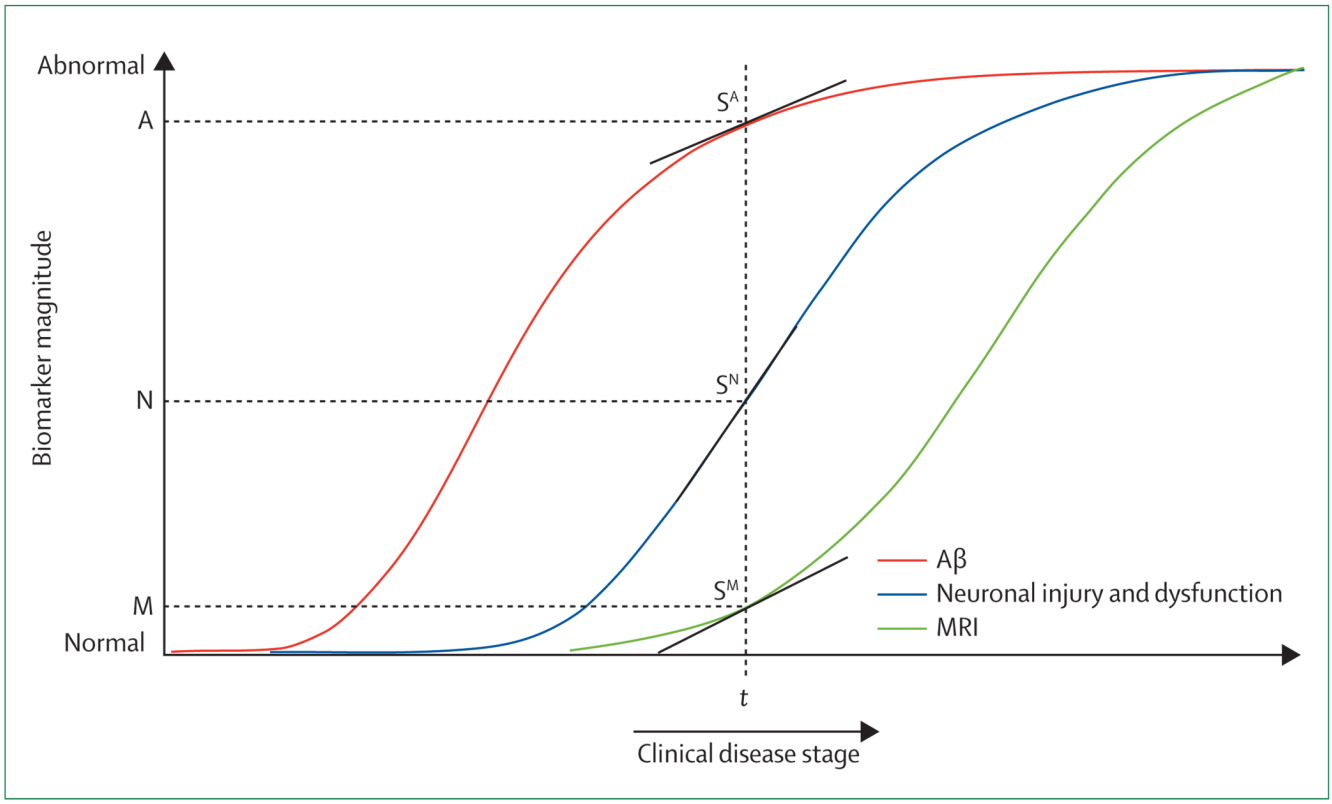

Figure 3. Staging Alzheimer's disease with dynamic biomarkers

Disease stage based on biomarkers is described by the magnitude of the biomarker abnormality and its rate of change at a given point in time (*t*). This is illustrated by the following terms: A (*t*)=magnitude of the Aβ plaque biomarker at time *t*; $S^A(t)$=slope of the Aβ plaque function at time *t*; N(*t*)=tau-mediated neuron injury at time *t*; $S^N(t)$=slope of N(*t*); M(*t*)=MRI at time *t*; $S^M(t)$=slope of M(*t*). Aβ=β-amyloid.

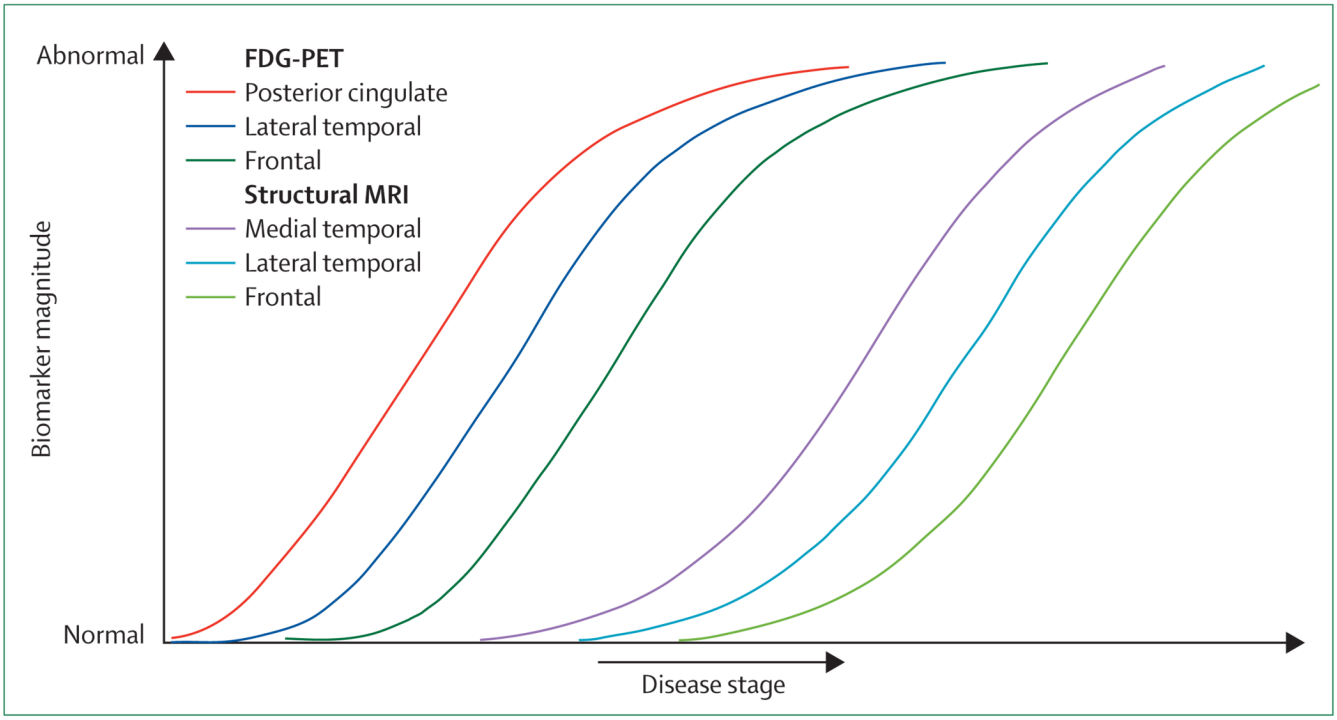

Figure 4. Anatomical imaging information

For simplicity in other figures, imaging biomarkers have been shown as individual curves. However, anatomical variation exists in the time courses within each imaging mode. For example, in FDG-PET, one would expect abnormalities to appear in the following order: precuneus/posterior cingulate, lateral temporal, and frontal lobe much later. Similarly, in structural MRI, one would expect abnormalities to appear in the following order: medial temporal, lateral temporal, and frontal lobe later. FGD=fluorodeoxyglucose.

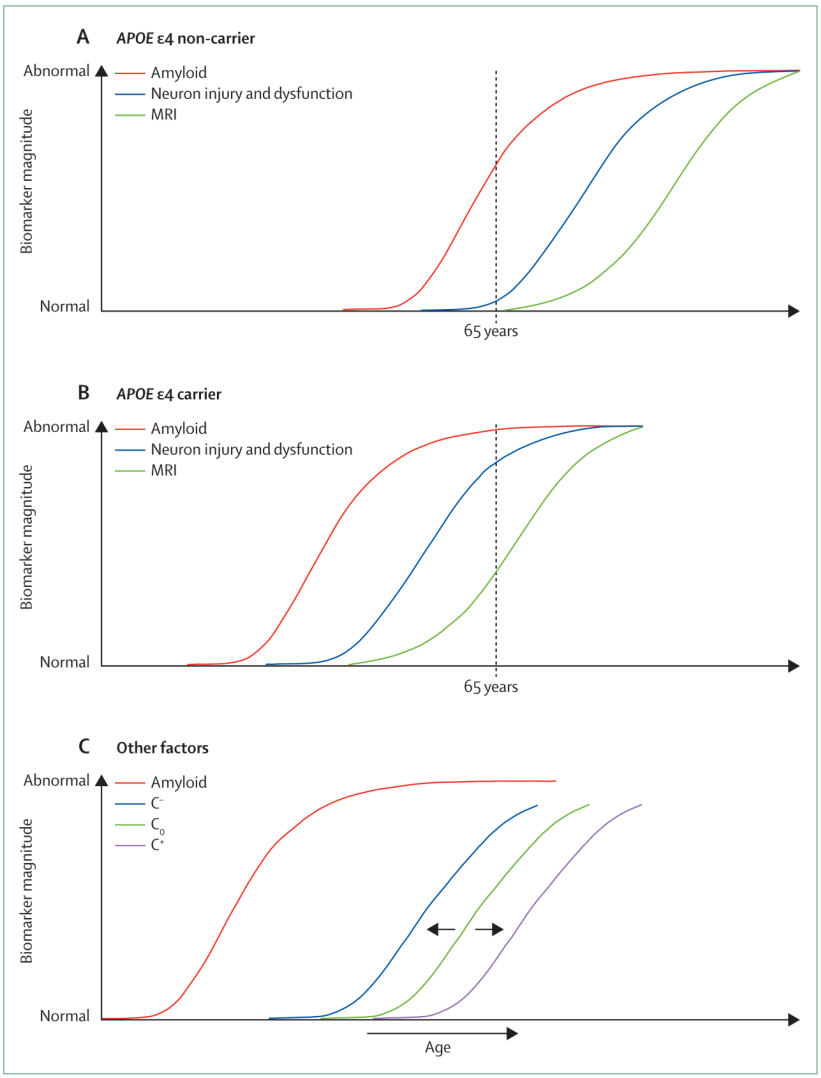

Figure 5. Modulators of biomarker temporal relationships

(A,B) Relative to a fixed age (here, 65 years), the hypothesised effect of *APOE* ε4 is to shift β-amyloid plaque deposition and the neurodegenerative cascade both to an earlier age compared with ε4 non-carriers. (C) The hypothesised effect of the presence of different diseases and genes on cognition: C^{-}=cognition in the presence of comorbidities (eg, Lewy bodies or vascular disease) or risk amplification genes; C^{+}=cognition in patients with enhanced cognitive reserve or protective genes; C_o=cognition in individuals without comorbidity or enhanced cognitive reserve.

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Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia:

A Meta-analysis

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Correction: This article was corrected online May 19, 2015, to fix curves in Figure 3C.

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Abstract

IMPORTANCE—Cerebral amyloid-β aggregation is an early pathological event in Alzheimer disease (AD), starting decades before dementia onset. Estimates of the prevalence of amyloid pathology in persons without dementia are needed to understand the development of AD and to design prevention studies.

OBJECTIVE—To use individual participant data meta-analysis to estimate the prevalence of amyloid pathology as measured with biomarkers in participants with normal cognition, subjective cognitive impairment (SCI), or mild cognitive impairment (MCI).

DATA SOURCES—Relevant biomarker studies identified by searching studies published before April 2015 using the MEDLINE and Web of Science databases and through personal communication with investigators.

STUDY SELECTION—Studies were included if they provided individual participant data for participants without dementia and used an a priori defined cutoff for amyloid positivity.

DATA EXTRACTION AND SYNTHESIS—Individual records were provided for 2914 participants with normal cognition, 697 with SCI, and 3972 with MCI aged 18 to 100 years from 55 studies.

MAIN OUTCOMES AND MEASURES—Prevalence of amyloid pathology on positron emission tomography or in cerebrospinal fluid according to AD risk factors (age, apolipoprotein E [*APOE*] genotype, sex, and education) estimated by generalized estimating equations.

RESULTS—The prevalence of amyloid pathology increased from age 50 to 90 years from 10% (95% CI, 8%-13%) to 44% (95% CI, 37%-51%) among participants with normal cognition; from 12% (95% CI, 8%-18%) to 43% (95% CI, 32%-55%) among patients with SCI; and from 27% (95% CI, 23%-32%) to 71% (95% CI, 66%-76%) among patients with MCI. *APOE*-ε4 carriers had 2 to 3 times higher prevalence estimates than noncarriers. The age at which 15% of the participants with normal cognition were amyloid positive was approximately 40 years for *APOE*ε4ε4 carriers, 50 years for ε2ε4 carriers, 55 years for ε3ε4 carriers, 65 years for ε3ε3 carriers, and 95 years for ε2ε3 carriers. Amyloid positivity was more common in highly educated participants but not associated with sex or biomarker modality.

CONCLUSIONS AND RELEVANCE—Among persons without dementia, the prevalence of cerebral amyloid pathology as determined by positron emission tomography or cerebrospinal fluid findings was associated with age, *APOE*genotype, and presence of cognitive impairment. These findings suggest a 20- to 30-year interval between first development of amyloid positivity and onset of dementia.

Alzheimer disease (AD) is the most common cause of dementia, with a worldwide prevalence of about 25 million in 2010, expected to be doubled by 2030 because of increased life expectancy.[1] The earliest recognizable pathological event in AD is cerebral amyloid-β aggregation.[2] This pathology may be present up to 20 years before the onset of dementia.[3,4] Novel research criteria for AD in individuals without dementia emphasize the presence of amyloid pathology to define the first stage of the disease.[5,6]

Prevalence estimates of amyloid pathology in persons without dementia are needed to better understand the development of AD and to facilitate the design of AD prevention studies. Initiation of treatment for AD in the predementia phase, when neuronal damage is still limited, may be crucial to have clinical benefit.[7] Neuropathological studies have reported prevalences of amyloid pathology in nondemented individuals ranging between 10% and 60%.[8,9] Studies that assessed amyloid pathology in nondemented individuals during life using biomarkers in cerebrospinal fluid (CSF) or on positron emission tomography (PET) also showed large variability in prevalence estimates (10%-70%).[10-13] This variability may have resulted from small sample sizes, differences in study design, and participant selection.

The aim of this study was to estimate the prevalence of amyloid pathology as assessed by biomarkers in nondemented individuals with an individual participant metaanalysis. We estimated the prevalence in participants with normal cognition, subjective cognitive impairment (SCI), and mild cognitive impairment (MCI) and investigated the relation with known risk factors for AD-type dementia, including age, sex, education, and *APOE* genotype. We also tested the association of biomarker modality and recruitment strategies with prevalence estimates and compared age-specific estimates of amyloid positivity in participants with normal cognition with the prevalence of AD-type dementia in the general population.

Methods

To identify relevant biomarker studies, the MEDLINE and Web of S c ience databases were searched for studies published before April 2015. The search terms used for PET studies were *PET* and (*Pittsburgh* or *PiB* or *florbetapir* or *AV-45* or *florbetaben* or *flutemetamol*) and (*amyloid* or *abeta*). The search terms used for CSF studies were (*CSF* or *cerebrospinal fluid*) and (*amyloid* or *abeta*). Titles and abstracts were reviewed and relevant studies were retrieved. Searches were restricted to articles published in the English language. Studies were included if amyloid biomarker data for participants without dementia were reported and an a priori defined cutoff for amyloid abnormality was used. Studies that included participants with neurological, psychiatric, or other diseases that might affect the central nervous system were excluded. We also asked partners from 2 European multicenter

collaborative projects, BIOMARKAPD and EMIF-AD, to provide unpublished data (Figure 1).

As most published studies did not provide prevalence estimates according to age and other risk factors, we asked study contact persons to provide participant-level data or tabulated data according to 10-year age categories and unpublished data if available. Tabulated data were converted to participant-level data with the average age in the age category. The quality of primary articles from each study was systematically assessed using relevant criteria from the STROBE[14] and QUADAS[15] guidelines (eTable 1 in the Supplement). All participants gave written informed consent to participate. Studies were approved by the local ethics committees of the participating centers.

Data Collection and Operationalization

Information on study procedures was extracted from the publication or requested from the study contact person and used to create a common set of variables.

Cognitive Status, *APOE*, Sex, and Education—Normal cognition was defined as normal scores on cognitive tests, the absence of cognitive complaints for which medical help was sought, or both. Subjective cognitive impairment was defined as presence of a cognitive complaint with presentation at a health care facility but normal cognition on tests. Mild cognitive impairment was defined according to published criteria.[16,17] These include a decline in memory or another cognitive domain reported by the patient, informant, or both and objectively verified by neuropsychological testing, in combination with no or minimal impairment in activities of daily living and not meeting criteria for dementia. Mild cognitive impairment was subclassified as amnestic MCI or nonamnestic MCI when possible. Information on *APOE*-ε4 carrier status (yes/no), *APOE* genotype, and years of education was retrieved. To describe the association of *APOE* genotype with age, we reported for each genotype the age at which 15% of the participants with normal cognition were amyloid positive as a proxy for first appearance of abnormal amyloid.

Setting and Recruitment—The study setting was classified as clinical if patients presented with cognitive complaints at a health care facility; research if patients were asked to participate in research by recruitment through advertisements or from other hospital departments; population-based if a random sample of the general population was included; or mixed if participants were recruited from a combination of settings.

Amyloid Assessment—Measurement details documented included amyloid tracer and assessment via visual scales or quantitative measures for PET studies and assay used to measure amyloid-$\beta_{1\text{-}42}$ levels for CSF studies. Positron emission tomography and CSF biomarkers were dichotomized as negative (normal) or positive (abnormal) according to study-specific cutoffs. (See eTables 2 and 3 in the Supplement for measurement details.) For participants who had both PET and CSF amyloid measures, we selected the first amyloid measure in time.

Comparison With Prevalence of AD-Type Dementia—Age- and *APOE*-specific prevalence data of AD-type dementia were obtained through a meta-analysis or from

published lifetime risk data for AD-type dementia[18] as described in the eMethods in the Supplement.

Number Needed to Screen—To use the prevalence estimates in selecting participants at risk for amyloid positivity for AD prevention studies, numbers needed to screen to identify 1 amyloid-positive participant were calculated as described in the footnote of eTable 6 in the Supplement.

Statistical Analysis

We conducted a meta-analysis with individual participant data, in which original research data were sought directly from study contact persons, combined, and reanalyzed centrally. Generalized estimating equations (GEEs) were used to estimate the prevalence and odds ratios (ORs). Generalized estimating equations allow for analysis of binary correlated data such that participant-level data on the prevalence from all studies could be modeled while simultaneously accounting for the clustering of participants within studies. We assumed a logit link function for binary outcome with an exchangeable correlation structure to account for within-study correlation. Analyses were performed using SPSS version 20.0 (IBM) with the genlin command. They were conducted using the total study population unless specified otherwise.

The main analyses were performed with cognitive status (normal cognition, SCI, MCI), age, sex, education, and *APOE*-ε4 genotype as independent variables. Age was entered as a continuous measure centered at the median. Educational level was dichotomized at the median (high, ≥14 years, vs moderate to low, <14 years). Secondary analyses tested associations with biomarker modality, MCI subtype, published vs unpublished studies, setting, and recruitment strategy while adjusting for cognitive status, age, and *APOE*-ε4 carrier status. We tested 2-way and 3-way interactions between variables and age as a quadratic term, and these were retained in the equation in case of a significant Wald statistic as indicated in table footers and figure legends. Analyses were repeated using natural cubic splines with knots at ages 50, 60, 70, and 80 years, but this did not improve the model. Estimated probabilities and 95% confidence intervals from the GEE analyses were used in tables. Probabilities estimated by GEE were compared with the observed probabilities in 5-year age groups.

The extent of between-study variability was investigated in several ways. In the total sample, the random intercept variance related to study was estimated in a random-effects analysis w ith the independent variables age, *APOE*-ε4 carrier status, cognitive status, and interactions using the xtmelogit function from Stata version 12.0 (Stata-Corp). This variance was expressed as an intraclass correlation coefficient. In diagnostic and *APOE* subgroups, heterogeneity within 5-year age strata was assessed with the I^2 statistic[19] from a random-effects meta-analysis in Stata version 12.0. An I^2 statistic value greater than 50% was considered indicative for substantial heterogeneity.[19] Center variability across the age range was visualized by plotting the prevalence for studies with more than 50 participants.

Significance level was set at $P < .05$ in 2-sided tests, uncorrected for multiple comparisons. When associations changed after correcting for multiple comparisons with the Bonferroni

method, this was mentioned in the text or table. R version 3.1.2 (R Foundation for Statistical Computing) and GraphPad Prism version 6.0 (GraphPad Software) were used for graphs with estimated probabilities and 95% confidence intervals from the GEE analyses.

Results

The literature search resulted in 7578 publications; amyloid was assessed by PET in 890 and by CSF in 6688. From these, 599 were selected for full-text review. We identified 47 studies from the European multicenter projects (Figure 1). A total of 91 unique studies met inclusion criteria; the authors of 55 studies agreed to share data. Contact persons from 54 studies provided participant-level data and 1 provided tabulated data (n = 137). Of the 36 studies for which contact persons refused or did not reply, 31 were selected through the literature search and 5 from the European multicenter studies. Characteristics of the 31 excluded published studies did not differ from those of the 55 included studies (eTable 4 in the Supplement).

Study Characteristics

Of the selected studies, 45 were single-center and 10 were multicenter studies. (eTable 5 in the Supplement shows detailed study information.) Forty-one studies provided data for participants with normal cognition, 20 for patients with SCI, and 47 for patients with MCI. Of the MCI studies, 8 classified patients with MCI as amnestic MCI or nonamnestic MCI, 10 studies only included patients with amnestic MCI, and all other studies used a broad MCI definition or did not specify MCI subtype. Information on *APOE*-ε4 carrier status was provided by 41 studies and information on *APOE* genotype by 37 studies. All studies but 1 specified the sex of the participants. Information on years of education was available from 44 studies. Studies contributing data for participants with normal cognition were performed in a research setting in 95% (n = 39, selection through advertisements in 15, from hospitals in 10, and from other or unknown sources in 14) and a mixed setting in 5% (n = 2). Forty-six of the studies (98%) that included patients with SCI or MCI were performed in a clinical setting.

Amyloid-PET data were provided by 29 studies. Of these, 22 studies used [^{11} C]Pittsburgh compound-B (PiB), 9 [^{18}F]florbetapir, 2 [^{18}F]florbetaben, and 1 [^{18}F]flutemetamol, including 5 that used multiple tracers. Eleven studies assessed the PET images by visual scales whereas 16 studies used quantitative assessment and 2 studies used both methods. Cerebrospinal fluid amyloid-β_{1-42} data were provided by 31 studies. The Innotest enzyme-linked immunosorbent assay (Fujirebio Europe) was used for CSF analysis in 29 studies and the xMAP Luminex assay in 2 studies. Two studies (1111 participants) provided data on both PET and CSF amyloid measures. Primary studies were assessed with the quality rating c riteria, and typic ally met all c riteria, although bias could not be assessed in 37 publications and participant flow remained unclear in 2 publications (eTable 1 in the Supplement).

Participant Characteristics

We included 7583 participants from 55 studies, of whom 2914 (38%) had normal cognition, 697 (9%) SCI, and 3972 (52%) MCI. Amyloid positivity was assessed with PET for 2370 participants (31%; 1346 normal cognition, 35 SCI, 989 MCI) and with CSF for 5213 participants (69%; 1568 normal cognition, 662 SCI, 2983 MCI). Baseline characteristics according to cognitive status are shown in Table 1. Participants with missing *APOE* data did not differ in amyloid positivity and sex from participants with *APOE* data but more often had limited education (63%) compared with participants who had these data available (48%, $\chi = 62.5$, $P < .001$). Participants with missing sex or education data did not differ in amyloid positivity, sex or education, and *APOE*-ε4 carrier status from participants with these data.

Prevalence of Amyloid Positivity

Estimated probabilities of amyloid positivity according to cognitive status, *APOE*-ε4 status, and age are displayed in **Figure 2**, **Figure 3**A and B, and **Table 2**. Observed prevalence estimates are shown in **Table 3**. The difference between the observed and predicted prevalence rates was less than 10% in more than 90% of the comparisons indicating good model fit. Amyloid positivity was about twice as common in patients with MCI compared with participants with normal cognition (mean difference, 25% [95% CI, 22% to 28%]; $P < .001$) or SCI (mean difference, 23% [95% CI, 14% to 32%]; $P < .001$), while it did not differ between participants with normal cognition and SCI (mean difference, 2% [95% CI, −6% to 10%]; $P = .62$). Amyloid positivity increased with age in all diagnostic groups.

APOE-ε4 carriers had 10% to 40% higher absolute prevalence estimates than noncarriers in each diagnostic group (Table 2, Figure 3A and B). At the median age of 70 years, the prevalence estimates were different between all *APOE* genotypes in participants with normal cognition, except for those of the ε2ε4 and ε3ε4 genotypes, which did not differ from each other (mean difference ε4ε4 vs ε3ε4, 38% [95% CI, 22% to 53%]; $P < .001$, vs ε2ε4, 28% [95% CI, 7% to 49%]; $P = .008$, vs ε3ε3, 60% [95% CI, 44% to 75%]; $P < .001$, vs ε2ε3, 73% [95% CI, 58% to 87%]; $P < .001$; mean difference ε3ε4 vs ε2ε4, 9% [95% CI, −1% to 20%]; $P = .08$, vs ε3ε3, 22% [95% CI, 18% to 26%]; $P < .001$, vs ε2ε3, 35% [95% CI, 29% to 40%]; $P < .001$; mean difference ε2ε4 vs ε3ε3, 31% [95% CI, 21% to 42%]; $P < .001$, vs ε2ε3, 44% [95% CI, 31% to 57%]; $P < .001$; mean difference ε3ε3 vs ε2ε3, 13% [95% CI, 8% to 17%]; $P < .001$) (Figure 3C).

After correction for multiple comparisons, ε2ε4 and ε4ε4 showed no statistically significant difference ($P = .08$). None of the 10 participants with ε2ε2 were amyloid positive. *APOE* genotype was associated with the age at onset of amyloid positivity. For example, the age at which 15% of the participants with normal cognition were amyloid positive was approximately 40 years for ε4ε4 carriers, 50 years for ε2ε4 carriers, 55 years for ε3ε4 carriers, 65 years for ε3ε3 carriers, and 95 years for ε2ε3 carriers. In patients with SCI, prevalence of amyloid pathology according to *APOE* genotype was similar to participants with normal cognition in all age groups (mean difference, 1% [95% CI, −11% to 12%]; $P = .92$). In patients with MCI, the prevalence differed between genotypes at the median age of 70 years, while again the ε2ε4 and ε3ε4 genotypes did not differ from each other; the difference between the ε2ε4 and ε3ε3 genotypes was not statistically significant (mean

difference ε4ε4 vs ε3ε4, 23% [95% CI, 17% to 29%]; $P < .001$, vs ε2ε4, 33% [95% CI, 14% to 51%]; $P = .001$, vs ε3ε3, 54% [95% CI, 47% to 60%]; $P < .001$, vs ε2ε3, 64% [95% CI, 57% to 71%]; $P < .001$; mean difference ε3ε4 vs ε2ε4, 10% [95% CI, −9% to 28%]; $P = .31$, vs ε3ε3, 31% [95% CI, 25% to 37%]; $P < .001$, vs ε2ε3, 41% [95% CI, 34% to 48%]; $P < .001$; mean difference ε2ε4 vs ε3ε3, 21% [95% CI, −1% to 43%]; $P = .06$, vs ε2ε3, 31% [95% CI, 9% to 53%]; $P = .005$; mean difference ε3ε3 vs ε2ε3, 10% [95% CI, 6% to 14%]; $P < .001$) (Figure 3D).

Patients with MCI and the APOE ε2ε2 genotype were not included in the analysis because of the small sample size (n = 5, of whom 1 was amyloid positive). The prevalence of amyloid pathology in patients with MCI at age 70 years was 89% (95% CI, 81%-94%) for ε4ε4 carriers, 66% (95% CI, 60%-72%) for ε3ε4 carriers, 57% (95% CI, 35%-76%) for ε2ε4 carriers, 35% (95% CI, 31%-40%) for ε3ε3 carriers, and 25% (95% CI, 19%-32%) for ε2ε3 carriers. **Table 4** shows the ORs for amyloid positivity of the *APOE* genotypes relative to the ε3ε3 genotype at age 70 years for participants with normal cognition and MCI.

The prevalence of amyloid pathology at the mean age was 5% higher (95% CI, 1% to 8%; $P = .005$) in participants with an education above the median (n = 2530) than in those with education below the median (n = 2415) regardless of cognitive status, age, and *APOE*-ε4 carrier status (eFigure 1 in the Supplement). There was no significant association with or interaction between sex and any of the risk factors for amyloid positivity (mean difference, 1% [95% CI, −1% to 3%]; $P = .52$).

Comparison With Prevalence of AD-Type Dementia

The age-related increase in amyloid positivity in participants with normal cognition paralleled age-specific AD-type dementia prevalence estimates, with an intervening period of about 20 years (**Figure 4**A). Similarly, *APOE* genotype–specific estimates of amyloid positivity paralleled *APOE* genotype–specific lifetime risks of AD-type dementia with a difference of 25 to 30 years (Figure 4B).

Number Needed to Screen

The numbers of participants needed to screen (NNS) to identify 1 amyloid-positive person are displayed according to age, cognitive status, and *APOE* genotype in eTable 6 in the Supplement. The NNS varied from 1.0 (95% CI, 1.0-1.1), for persons with normal cognition or MCI who were older than 70 years with the *APOE* ε4ε4 genotype, to 16.7 (95% CI, 11.1-25.0), for persons with normal cognition aged 50 years without an *APOE*-ε4 allele. If *APOE* genotype is unknown, participants need to be screened for this first. The number of participants for whom *APOE* genotyping needs to be performed to find 1 participant with that particular *APOE* genotype who is amyloid positive varied between 3.5 (95% CI, 2.8-4.3), for persons with normal cognition aged 90 years without an *APOE*-ε4 allele, to 89.6 (95% CI, 64.5-129.0), for persons with normal cognition aged 50 years with the *APOE*ε4ε4 genotype.

Assessment of Study-Related Heterogeneity

In the total study population, the intraclass correlation coefficient for study-related random intercept variance was 0.085, indicating minor heterogeneity among studies. Within age, *APOE*-ε4, and diagnostic subgroups, heterogeneity was not substantial according to the I^2 statistic, except for 2 of 54 subgroups (50%-60% in age group 65-69 years of SCI *APOE*-ε4 carriers and in age group 75-79 years of MCI *APOE*-ε4 noncarriers) (eTable 7 in the Supplement).

Visual inspection of variability in prevalence estimates across age in studies with at least 50 participants also indicated that between-study variability was small (eFigure 2 in the Supplement).

Post Hoc Analyses

The biomarker used to assess amyloid positivity was not associated with prevalence (mean difference, 0% [95% CI, −7% to 8%]; $P = .87$) for participants with normal cognition or MCI (n = 6885). Patients with SCI were excluded because amyloid was measured with PET in only 5% of participants. While adjusting for *APOE*-ε4 carrier status and age, amyloid prevalence at the mean age was higher in patients with amnestic MCI (n = 1405) than in patients with nonamnestic MCI (n = 225, 58% [95% CI, 48% to 67%] vs 47% [95% CI, 35% to 60%], mean difference, 11% [95% CI, 0% to 21%]; $P = .03$) and higher in patients with nonamnestic MCI than in participants with normal cognition (n = 2289, mean difference, 15% [95% CI, 2% to 28%]; $P = .03$). The prevalence did not differ between amnestic MCI (n = 1405) and MCI patients diagnosed using a broad or unspecified definition of MCI (n = 1487, mean difference, 3% [95% CI, −6% to 13%]; $P = .51$). Prevalence estimates did not differ for published and unpublished studies (eTable 8 in the Supplement). The prevalence in participants with normal cognition recruited via advertisements (n = 1868) was similar to that of participants recruited from hospital departments (n = 305, mean difference, 4% [95% CI, −13% to 21%]; $P = .96$).

Discussion

This amyloid biomarker study including individuals without dementia provides prevalence estimates of amyloid pathology over an age range of 18 to 100 years for persons with normal cognition, SCI, and MCI. The age at onset of amyloid positivity was associated with cognitive status and the *APOE* genotype. At age 90 years, about 40% of the *APOE*-ε4 noncarriers and more than 80% of *APOE*-ε4 carriers with normal cognition were amyloid positive. Amyloid positivity was associated with education but not with sex or biomarker modality. The age-related prevalence of amyloid positivity in participants with normal cognition paralleled the age-related prevalence of AD-type dementia in the general population in an *APOE* genotype–specific way with a time lag of 20 to 30 years.

Patients with MCI had 20% to 30% higher prevalence estimates of amyloid positivity than those with normal cognition or SCI, supporting the view that MCI is a risk state for AD.[16] Cognitively normal and SCI groups did not differ in amyloid positivity, suggesting that the presence of SCI in a memory clinic population might not be associated with an increased

risk for AD. Previous studies in other settings showed inconsistent results regarding differences in amyloid positivity between cognitively normal and SCI participants,[20,21] indicating that further research is needed on this. Patients with nonamnestic MCI had lower prevalence estimates of amyloid positivity than patients with amnestic MCI but higher than participants with normal cognition. This suggests that both amnestic MCI and nonamnestic MCI are associated with an increased risk for AD and that this risk is higher for patients with amnestic MCI. The observation that a substantial number of patients with MCI were not amyloid positive, even at older age, suggests that the MCI phenotype does not always have AD as underlying pathology. Possible non-AD causes in MCI may be hippocampal sclerosis, mild depression, or vascular damage.

Age was a risk factor for amyloid positivity, which is in line with the finding that age is an important risk factor for postmortem amyloid load[22] and for AD-type dementia,[23] as also shown in Figure 4A. The prevalence of amyloid positivity in participants with normal cognition aged 50 to 60 years was somewhat higher than found in an earlier population-based study that was not included in our analysis.[24] This could relate to differences in recruitment strategy and assessment.

Relative to the *APOE*-ε3 allele, the *APOE*-ε4 risk allele was associated with a greater risk for amyloid positivity and de creased age at onset, while the *APOE*-ε2 allele had the opposite associations. This is similar to the relation of *APOE* genotype with the risk for AD-type dementia and age at onset of AD-type dementia as reported in clinical studies[25,26] and the *APOE* genotype–specific lifetime risk for AD as shown in Figure 4B. The high prevalence of amyloid positivity in participants with normal cognition and MCI with ε2ε4 in the present study indicates that the detrimental relation of amyloid positivity with ε4 outweighs the protective association with ε2, in line with clinical AD studies.[27] The OR for amyloid pathology of the *APOE* genotypes relative to the ε3ε3 genotype was similar to the OR for AD-type dementia in case-control studies.[18,27] The strong association of the *APOE* genotype with amyloid positivity emphasizes *APOE* as an important target for treatment studies.[28,29]

Highly educated participants had a higher prevalence of amyloid pathology than those with less formal education. This may seem in contrast with the finding that high education level is associated with a lower risk for AD-type dementia[30] but is in agreement with the cognitive reserve hypothesis.[31] According to this hypothesis, nondemented individuals with a high level of education have a greater cognitive reserve such that they can sustain more amyloid pathology before developing dementia. Education itself was not associated with the extent of pathology at postmortem examination[32] but might modify the relationship between AD pathology and expression of dementia,[33] resulting in higher amyloid positivity prevalence in nondemented highly educated participants. An alternative explanation would be that highly educated persons with amyloid pathology may be overrepresented in study participation or clinical care seeking due to self-selection bias.

Our finding that the prevalence of amyloid positivity was the same for men and women is in line with a previous neuropathological study showing no difference in neuritic and diffuse plaque load between men and women.[34] This finding is also in agreement with another

earlier study,[35] as is our finding that there was no interaction between sex and *APOE*-ε4 carrier status on amyloid positivity.

Although PET and CSF are thought to measure different types of amyloid-β,[36] we did not find differences in amyloid positivity estimates for PET and CSF biomarkers. This is in line with published high concordance rates of 84% to 92% between the 2 biomarkers.[37,38] Also, high levels of agreement have been reported for studies that provided more than 50 participants to our study in whom amyloid was assessed with both PET and CSF.[39,40]

We pooled data from a large number of studies, and this may have introduced bias because of differences in the methods underlying amyloid assessment, cutoff definition, participant selection, diagnostic criteria, and other aspects of study design. However, in the total study sample; in age, *APOE*, and diagnostic subgroups; and on visual inspection of study-specific prevalences over age, there was limited evidence for study-related heterogeneity, which supports the pooling of data from different studies (eFigure 2 and eTable 7 in the Supplement). Moreover, the Alzheimer's Association Quality Control program for CSF biomarkers reported that overall concordance for diagnostic classification was high between centers despite analytical variance.[41] We also explored the association of a number of study characteristics with the prevalence in post hoc analyses, but no relation was found. An advantage of participant-level analysis over aggregated pooling is that the power to detect subgroup effects is increased,[42] while the risk for ecological bias is decreased.[43]

A limitation of this study is that our participants with normal cognition were mostly recruited via advertisements, making this sample vulnerable to self-selection bias[44] and restricting generalizability to the general population. Participants with SCI and MCI were mostly recruited from clinical settings, rendering them dissimilar from these individuals in the general population. Participants with significant comorbid disorders are usually excluded from participation, and studies often used standardized cognitive screens, which also affects generalizability. Although MCI was not classified as amnestic or non-amnestic for most participants, our findings indicate that we mostly included amnestic MCI patients because the prevalence estimates in amnestic MCI patients did not differ from those with a broad or unspecified definition of MCI. Still, patients with nonamnestic MCI had a lower prevalence than patients with amnestic MCI, suggesting that this is an important distinction to make in future research. Moreover, our prevalence estimates are based on cross-sectional data. The life-time risk for individuals without dementia to develop amyloid pathology will be higher than the cross-sectional estimate at any age because amyloid-positive persons may die or progress to dementia at follow-up.

This study has several implications for understanding the development of AD. The observation that key risk factors for AD-type dementia are also risk factors for amyloid positivity in cognitively normal persons provides further evidence for the hypothesis that amyloid positivity in these individuals reflects early AD. Further support for this hypothesis comes from other studies that show that amyloid positivity in nondemented individuals is associated with memory impairment, cognitive decline, increased amyloid deposition and brain atrophy rates, and mortality.[45-48] Our study also indicates that development of AD pathology can start as early as age 30 years, depending on the *APOE*genotype. Comparison

with prevalence and lifetime risk estimates of AD-type dementia suggests a 20- to 30-year interval between amyloid positivity and dementia, implying that there is a large window of opportunity to start preventive treatments. Still, the exact interval between the onset of amyloid positivity and onset of AD-type dementia needs to be assessed by long-term follow-up studies because not all persons with amyloid pathology will become demented during their lifetime,[49] and not all individuals with a clinical diagnosis of AD-type dementia have amyloid pathology. Because of the uncertainty about whether and when an amyloid-positive individual without dementia will develop dementia, amyloid positivity in these individuals should not be equated with impending clinical dementia but rather be seen as a risk state. Our prevalence rates can be used as an inexpensive and noninvasive approach to select persons at risk for amyloid positivity.

Conclusions

Among persons without dementia, the prevalence of cerebral amyloid pathology as determined by PET imaging or CSF findings was associated with age, *APOE* genotype, and presence of cognitive impairment. These findings suggest a 20- to 30-year interval between first development of amyloid positivity and onset of dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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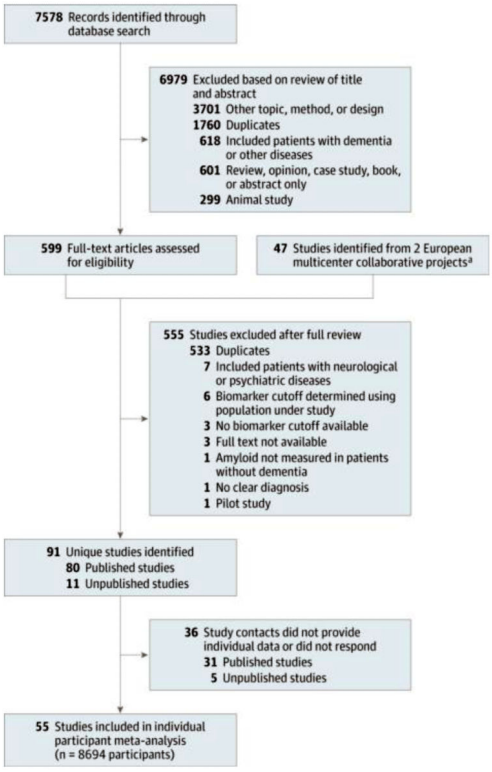

Figure 1.

Flow Diagram of Literature Search and Study Selection

[a] The European Medical Information Framework–Alzheimer Disease (EMIF-AD) and Biomarkers for Alzheimer Disease and Parkinson Disease (BIOMARKAPD) projects.

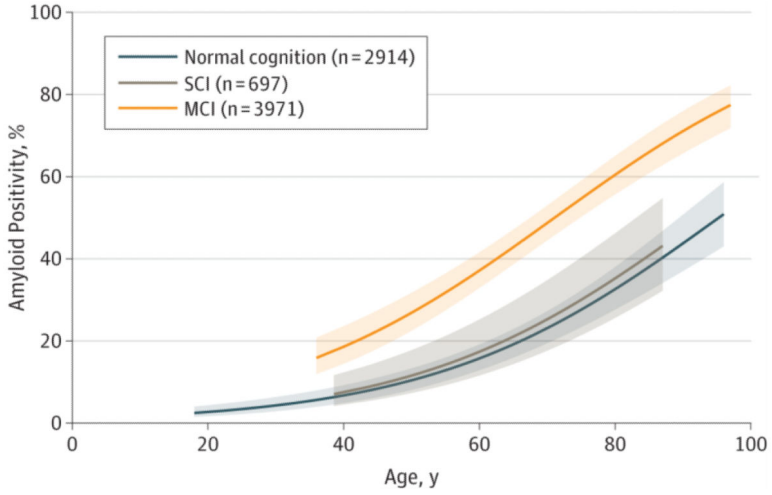

Figure 2.

Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status

The prevalence estimates were generated from generalized estimating equations. The model included age and cognitive status as predictors. Shading indicates 95% CIs; SCI, subjective cognitive impairment; MCI, mild cognitive impairment.

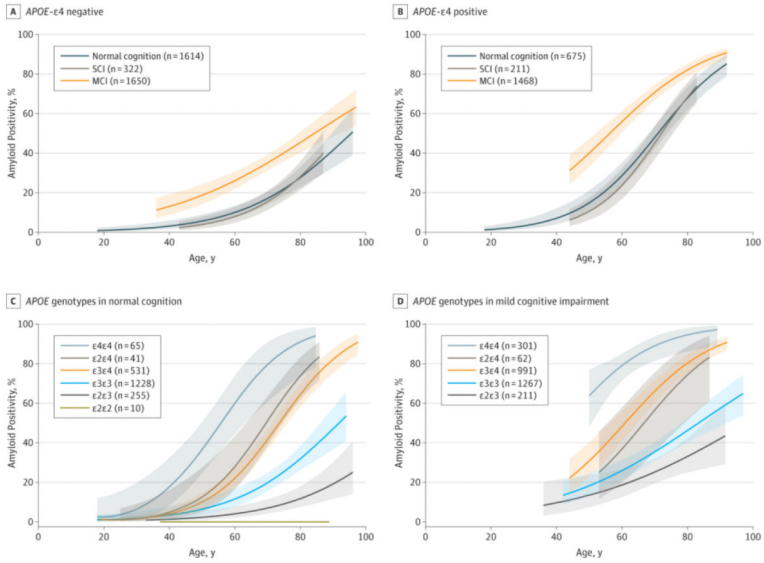

Figure 3.

Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status and Apolipoprotein E *(APOE)* Genotype

The model for the analyses in panels A and B included age, cognitive status, *APOE*-ε4 status, an interaction between age and cognitive status, and an interaction between age and *APOE*-ε4 status as predictors. The models for the analyses in panels C and D included age, cognitive status, *APOE* genotype, an interaction between age and cognitive status, an interaction between age and *APOE* genotype, and an interaction between cognitive status and *APOE* genotype as predictors. In panel C, none of the 10 participants with ε2ε2 were amyloid positive, and no 95% confidence interval is provided for this group. In panel D, data of participants with ε2ε2 are not shown because of the small sample size (n = 5). Shading indicates 95% CIs; SCI, subjective cognitive impairment; MCI, mild cognitive impairment.

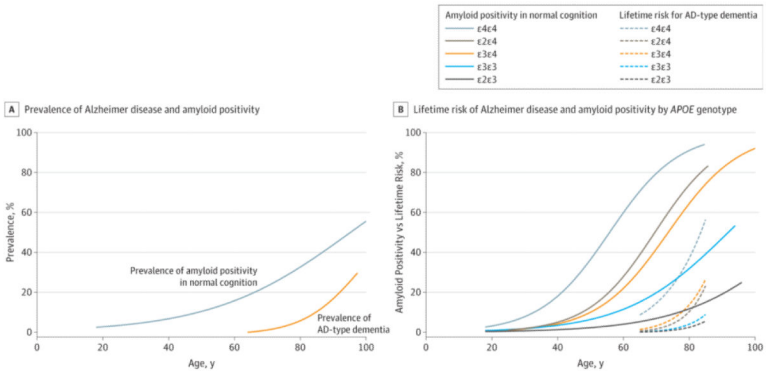

Figure 4.

Comparison of the Prevalence of Amyloid Positivity With the Prevalence of and Lifetime Risks for Alzheimer Disease–Type Dementia

The prevalence estimates in panel A were estimated from a meta-analysis of 14 studies (eMethods in the Supplement). The prevalence estimates in panel B of amyloid positivity in participants with normal cognition are plotted against published lifetime risks for Alzheimer disease (AD)–type dementia by *APOE* genotype (adapted from Genin et al[18]).

Table 1

Baseline Study Participant Characteristics

Charactrerstic	Normal Cognitiin (n = 2914)	SCI (n = 697)	MCI (n = 3972)
Age	(n = 2914)	(n = 697)	(n = 3971)
Mean (SD), y	66.8 (13.2)	64.2 (8.0)	70.2 (8.7)
Age groups, No. (%), y			
<40	140 (4.3)	1 (0.1)	1 (0.0)
40-44	28 (1.0)	3 (0.4)	10 (0.3)
45-49	80 (2.7)	12 (1.7)	31 (0.8)
50-54	178 (6.1)	48 (6.9)	113 (2.8)
55-59	258 (8.9)	158 (22.7)	349 (8.8)
60-64	361 (12.4)	170 (24.4)	541 (13.6)
65-69	530 (18.2)	126 (18.1)	763 (19.2)
70-74	567 (19.5)	103 (14.8)	333 (22.2)
75-79	380 (13.0)	56 (8.0)	745 (18.8)
80-84	263 (9.0)	16 (2.3)	385 (9.7)
85-89	102 (3.5)	4 (0.6)	131 (3.3)
≥90	27 (0 9)	0	19 (0.5)
Sex, No. (%)	(n = 2796)	(n = 697)	(n = 3972)
Female	1537 (55.0)	348 (49.9)	1339 (46.3)
Male	1259 (45.0)	349 (50.1)	2133 (53.7)
Education	(n = 2280)	(n = 364)	(n = 2926)
Mean (SD), y	14.6 (3.6)	12.1 (4 3)	12.5 (4.4)
Education by category, No. (%)	(n = 2280)	(n = 539)	(n = 3099)
<14 y	815 (35.7)	356 (66.0)	1854 (59.8)
≥14 y	1465 (64.3)	183 (34.0)	1245 (40.2)
MMSE score[a]	(n = 2592)	(n = 693)	(n = 3910)
Mean (SD)	29.0 (1.3)	28.4 (1 5)	26.8 (2.5)
Assessment by PET biomarker	1346 (46.2)	35 (5.0)	989 (24.8)

Charactrerstic	Normal Cognitiin (n = 2914)	SCI (n = 697)	MCI (n = 3972)
Assessment by CSF biomarker	1568 (53.8)	662 (95.0)	2983 (75.2)
Bromarker abnormal. No. (%)			
Anylold PET	326 (24.4)	8 (22.8)	523 (52.9)
CSF β amyloid	415 (26.5)	144 (21.8)	1513 (50.7)
APOE-ε4 carrier status. No. (%)	(n = 2289)	(n = 533)	(n = 3118)
APOE-ε4 negative	1614 (70.5)	322 (60.4)	1650 (52.9)
APOE-ε4 Positive	675 (29.5)	211 (39 6)	1468 (47.1)
APOE genotype, No. (%)	(n = 2130)	(n = 533)	(n = 2837)
ε2ε2	10 (0 5)	1 (0.2)	5 (0.2)
ε2ε3	255 (12.0)	49 (9.2)	211 (7.4)
ε2ε4	41 (1 9)	13 (2.4)	62 (2.2)
ε3ε3	1228 (57.7)	272 (51.0)	1267 (44.7)
ε3ε4	531 (24.9)	178 (33.4)	991 (34.9)
ε4ε4	65 (3 1)	20 (3.8)	301 (10.6)

Abbreviations: *APOE*, apolipoprotein E; CSF,cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; PET, positron emission tomography; SCI, subjective cognitive impairment.

[a] Range 0-3O. with 30 as the best Score.

Table 2

Prevalence Estimates of Amyloid Positivity According to Age, Cognitive Status, and *APOE*-ε4 Carrier Status[a]

	Normal Cognition, %(95%CI)			SCI, % (95% CI)			MCI, % (95% CI)		
Age, y	**Total**	***APOE*-ε4−**	***APOE*-ε4+**	**Total**	***APOE*-ε4−**	***APOE*-ε4+**	**Total**	***APOE*-ε4−**	***APOE*-ε4+**
50	10.4 (8.1-13.3)	5.7 (3.6-8.9)	14.9 (10.2-21.2)	11.6 (7 3-17.8)	3.9 (1.9-7.8)	10.6 (6.2-17.5)	26.9 (22.5-31.7)	18.7 (14.2-24.2)	40.0 (33.2-47.2)
55	12.9 (10.3-16.0)	7.6 (5.2-11.0)	20.9 (15.5-27.5)	14.2 (9 3-21.2)	5.6 (3.1-10.0)	16.1 (10.4-24.0)	31.8 (27.5-36.4)	22.2 (17.8-27.3)	47.9 (41.7-54.2)
60	15.8 (12.9-19 1)	10.0 (7.4-13 5)	28.6 (22.9-35.1)	17.4 (11.6-25.2)	8.0 (4.9-12.7)	23.7 (16.9-32.2)	37.1 (32.9-41.6)	26.1 (21.9-30.7)	55.9 (50.5-61.2)
65	19.2 (16.0-22 9)	13.2 (10.4-16.6)	37.8 (32.0-43.9)	21.1 (14.4-29.7)	11.2 (7.6-16 3)	33.5 (25.9-42.5)	42.8 (38.7-47.1)	30.4 (26.5-34.6)	63.6 (59.0-68.0)
70	23.1 (19.5-27 2)	17.1 (14.1-20.6)	47.9 (42.2-53.7)	25.3 (17.7-34.3)	15.5 (11.3-20.9)	45.0 (36.9-53.4)	48.7 (44.5-53.0)	35.1 (31.3-39.2)	70.7 (66.6-74.4)
75	27.6 (23.4-32 3)	21.9 (18.4-25.9)	58.2 (52.3-63.8)	30.0 (21.4-40.3)	21.2 (16.1-27.3)	57.1 (48.7-65.1)	54.6 (50.2-59.0)	40.1 (35.9-44.6)	76.9 (73.1-80.2)
80	32.6 (27.6-38.0)	27.7 (23.0-32.9)	67.8 (61.6-73.5)	35.2 (25.6-46.2)	28.1 (21.5-35.8)	71.5 (63.0-78.8)[b]	60.4 (55.7-65.0)	45.4 (40.2-50.7)	82.1 (78.5-85.2)
85	38.0 (32.2-44 2)	34.2 (27.7 41.4)	76.2 (69.8-81.6)	40.8 (30.3-52.3)	36.3 (27.3-46.4)	74.0 (65.5-81.0)[b]	66.0 (60.3-70.7)	50.7 (44.3-57.1)	86.3 (32.9-89.2)
90	43.8 (37.0-50.7)	41.5 (32.7-50.8)	82.9 (76.6-87.7)	43.1 (32.2-54.7)[b]	39.9 (29.7-51.0)[b]		71.1 (65.7-75.9)	56.1 (48.3-63.5)	89.1 (85.9-91.7)[b]

Abbreviations; *APOE,* apolipoprotein E; MCI, mild cognitive impairment; SCI, subjective cognitive impairment.

[a]The prevalence estimates were generated from generalised estimating equations. Amyloid positivity in the total group was modeled using age and cognitive status as predictors. Amyloid positivity according to *APOE*-ε4 status was modeled with age, cognitive status, *APOE*-ε4 status, an interaction between age and cognitive status, and an interaction between age and *APOE*-ε4 status. Table 3 displays the number of participants and observed probabilities of amyloid positivity per age subgroup. Mo estimate was provided if the 5-year range around the indicated column age included no participants.

[b]No participants available with the exact age; prevalence estimated at nearest age.

Table 3

Observed Probabilities of Amyloid Positivity[a]

	Normal Cognition			SCI			MCI		
Age Group	**Total**	***APOE*-ε4−**	***APOE*-ε4+**	**Total**	***APOE*-ε4−**	***APOE*-ε4+**	**Total**	***APOE*-ε4−**	***APOE*-ε4+**
47 5-52.4 y	13.2 (15/114)	7.9 (5/63)	17.2 (5/29)	19.2 (5/26)	0.0 (0/8)	0.0 (0/8)	25.0 (16/64)	19.4 (7/36)	44.4 (8/18)
52 5-57.4 y	15.3 (38/249)	6.9 (8/116)	23.1 (15/65)	10.6 (12/113)	8 3 (4/48)	7.3 (3/41)	26.6 (78/293)	22.0 (24/109)	53.8 (42/78)
57 5-62.4 y	12.1 (36/296)	10.0 (16/160)	26.1 (12/46)	16.9 (29/171)	5 2 (5/96)	35.2 (19/54)	39.1 (181/463)	30.4 (58/191)	51.4 (95/185)
62 5-67.4 y	22.6 (110/485)	13.4 (31/232)	40.6 (54/133)	16.8 (24/143)	4 5 (3/66)	30.4 (14/46)	45.5 (303/666)	27.7 (74/267)	67.1 (171/255)
67 5-72.4 y	24.1 (128/53C)	17.1 (50/292)	40.7 (55/135)	26.0 (32/123)	16.1 (9/56)	42.9 (12/28)	54.5 (461/845)	35.0 (104/297)	77.1 (272/353)
72 5-77.4 y	32.2 (164/510)	23.3 (70/301)	61.3 (65/106)	44.0 (33/75)	25.0 (7/28)	59.3 (16/27)	57.2 (494/864)	44.4 (154/347)	79.1 (250/316)
77 5-82.4 y	42.0 (111/264)	35.1 (60/171)	65.5 (36/55)	31.8 (7/22)	33.3 (3/9)		62.1 (323/520)	49.2 (117/238)	86.9 (153/176)
82 5-87.4 y	49.0 (103/210)	41.7 (55/132)	76.5 (39/51)	57.1 (8/14)	50.0 (4/8)		60.3 (135/224)	51.4 (57/111)	81.9 (59/72)
87 5-92.4 y	51.0 (25/49)	42.9 (15/35)	87.5 (7/8)				61.4 (35/57)	58.5 (24/41)	1000 (7/7)

Abbreviations: *APOE*, apolipoprotein E; MCI, mild cognitive impairment; SCI, subjective cognitive impairment.

[a]Data are observed probabilities in % (No amyloid positive/No. total subgroup). No estimates were provided if the age group included <5 participants.

Table 4

Odds Ratios for the Association Between *APOE* Genotype and Amyloid Positivity at Age 70 Years[a]

	***APOE* Genotype**				
	ε3ε3	**ε2ε3**	**ε2ε4**	**ε3ε4**	**ε4ε4**
Normal cognition					
OR (95% CI)	1 [Reference]	0 34 (0.23-0.51)	4.29 (2.67-6.90)	2.94 (2.34-3.70)	18.76 (5.47-64.37)
P value		<.001	<.001	<.001	<.001
No amyloid positive (%)	275 (22.4)	22 (8.6)	17 (41.5)	213 (40.1)	45 (69.2)
MCI					
OR (95% CI)	1 [Reference]	0 59 (0.48-0.73)	2.38 (0.98-5.81)	3.52 (2.73-4.55)	14.50 (8.14-25.81)
P value		<.001	.06	<.001	<.001
No. amyloid positive (%)	490 (38.7)	57 (27.0)	35 (56.5)	666 (67.2)	261 (86.7)

Abbreviations: *APOE*, apolipoprotein E: OR, odds ratio; MCI, mild cognitive impairment.

[a]The ORs were generated from generalized estimating equations separately in participants with normal cognition and MCI. The models included age, *APOE* genotype, an interaction between age and *APOE* genotype, and a quadratic age term in the normal cognition model as predictors. *P* values represent the significance of the OR for amyloid pcsitivity compared with the ε3ε3 genotype. The ε2ε2 genotype was excluded because of the small number of participants in this group.

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Associative and recognition memory for novel objects in dementia: implications for diagnosis

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Abstract

It has been demonstrated that patients with dementia of the Alzheimer's type show particular difficulties with a task that measures memory for object locations [R. Swainson *et al*. (2001) *Dement. Geriatr. Cogn. Disord*. **12**, 265–80]. The present study followed on from this report by asking whether the deficits seen in dementia of the Alzheimer's type were specific to this condition, or whether they would also be seen in another common neurodegenerative syndrome, frontotemporal dementia. To investigate this important issue, we examined memory for object–location pairs and visual recognition memory for novel patterns using two tests, the Paired Associates Learning and Matching to Sample tasks, from the Cambridge Neuropsychological Testing Automated Battery. The performance of a subset of the patients with dementia of the Alzheimer's type described by Swainson *et al*., selected on the basis of age and education, was compared with matched groups of frontal variant frontotemporal dementia, semantic dementia and control subjects. In contrast to the patients with dementia of the Alzheimer's type, who showed significant impairment on both memory tests, the two frontotemporal dementia groups did not perform significantly poorer compared with control subjects on nearly all memory measures, other than 'memory score' from the paired associates learning task. These findings confirm that tests of episodic memory, especially for the location of objects in space, may be useful in the early diagnosis and differentiation of dementia of the Alzheimer's type.

Introduction

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Testing for nominal dysphasia

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SUMMARY In this paper we have described the construction of a graded naming test that makes the distinction between object and proper names. This distinction was prompted by a single case study of a patient who showed a specific naming impairment for a particular class of proper names. Naming vocabulary was found to be highly correlated with other measures of verbal intelligence and we have discussed the use of the graded naming test as a tool for clinical assessment and diagnosis. The results of the naming test of the left hemisphere group showed that category-specific naming impairment along the object/proper name distinction is relatively uncommon in any gross form. Object naming was most impaired in patients with lesions of the temporal lobe.

A reduced efficiency in retrieving the name of an object can be the first and only indication of impaired language functioning. This alone makes a sensitive test of naming ability essential for a clinician who wishes to detect the abnormality before it becomes merely a statement of the obvious.

Verbal abilities vary considerably from individual to individual in the general population so it is not unreasonable to assume that naming ability does also. Measures of general vocabulary level correlate highly with other measures of verbal and non-verbal intelligence[1] and it is probable that naming vocabulary skills may be similarly correlated. To date, tests for naming deficits have been based on global measures of current naming ability, such as number of failures or latencies of responses[2] without taking into account the possible effects of individual variations in optimal levels of functioning. The significance of an individual's present level of performance may be lost unless it can be considered in the context of his other cognitive skills. For example, if one accepts the commonly held view that less frequent items are more vulnerable to word-finding difficulties than better-established well-practised items[2-4] then an individual with an extensive naming vocabulary who develops mild word-finding difficulties may continue to function with no obvious abnormality when presented with items that are common and of high frequency in the context of his own vocabulary. The aim of the present study was to develop a naming test with items of graded difficulty which allows for individual differences in naming ability.

Evidence of category specificity in the cerebral organisation of language is beginning to emerge from recent studies of language disorders. Selective comprehension deficits and selective naming deficits that are category-specific have now been reported.[5-7] In a recent study, McKenna and Warrington[8] described a patient whose only *intact* naming competence was for the proper name class, countries. In the present study two major semantic categories were selected—object names and proper names. The choice of these particular categories was prompted by our previous single case study[8] and by the observations of a further patient who had a selective impairment for one class of proper names in an otherwise intact naming vocabulary. We report the neurological and psychological investigations of this patient in Appendix 1.

In the present study we describe the construction of two graded naming tests, for object names and proper names respectively. These tests were standardised on a group of 100 normal subjects, and subsequently a group of 46 patients with localised left hemisphere lesions were tested. The aims of our investigations were threefold:

(1) To examine the relationship between intelligence and naming ability in a normal population with a view to developing a clinically more useful test.

(2) To explore the incidence of specific naming deficits in the object and proper name categories in patients with left hemisphere lesions; and

(3) To obtain further evidence for the anatomical correlates of naming deficits.

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Construction and standardisation of the naming tests

Collection of item pool

Object and proper name items to meet the following criteria were collected:

(1) Items should be sufficiently distinctive to be presented in photographic or pictorial form (for example "sandpaper," "vinegar" would not be suitable).

(2) That the particular responses required should be immediately recognisable from the visual stimulus as being the single response desired, for example a drawing of a "crowd" or "coast" would be too open to misinterpretation and could invoke many responses, such as "people," "mob," "meeting," and "land," "shore," "seaside," etc.

(3) That the visual representation of the items as well as the verbal concept should be well known. This proved particularly difficult to achieve in choosing proper names, for example most authors, however famous, are unknown pictorially.

(4) That there should be stability over time such that the items have "staying power." Therefore many contemporary personalities were not considered suitable.

Following these criteria as closely as possible, a pool of 66 proper names and 61 object names were collected for standardisation.

Measures of intelligence

Obviously the most satisfactory measure of intelligence would have been a comprehensive IQ test such as the WAIS but time factors rendered such a project untenable. As a compromise the Vocabulary and Picture Completion subtests of the WAIS were given. These were chosen on the grounds that they are the verbal and performance scale subtests that correlate most highly with the full scale IQ. Also included were the Nelson and Schonell reading tests[9] on the grounds that previous studies[10 11] had shown these to be good indicators of level of intellectual functioning in normal subjects.

Procedure

One hundred volunteers ranging in age from 18 to 76 years acted as subjects. The great majority of these were patients with extracerebral diseases at the National Hospital. Only subjects who had been educated in the normal English system were included. The tests were given in one session, the WAIS subtests being followed by the reading tests and then the 61 object name items and the 66 proper name items.

Selection of test items

From the results obtained for the 61 object names and the 66 proper names, items that were too easy or too hard to produce good discrimination between the subjects were eliminated, as were items producing ambiguous responses (see criteria (II) for item selection). Thirty object name items and 30 proper name items were selected from the remainder to form two tests of graded difficulty (see Appendix II). The results of the 100 volunteer normal subjects on these two 30-item tests are shown in fig 1.

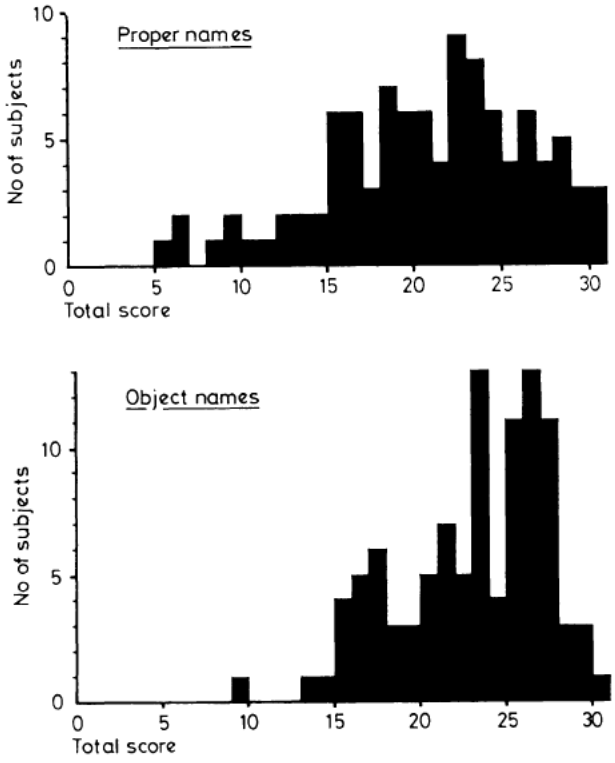

Fig 1 *Control subjects: distribution of scores on the Object Names Test and Proper Names Test.*

Results of standardisation

The correlations (product–moment) between each measure of intelligence and each score on the two naming tests are given in table 1.

It has already been established that scores on the WAIS Vocabulary and the Nelson and Schonell reading tests are highly intercorrelated[10 11] and the present study has shown high correlations between

Table 1 *Control subjects: product moment correlations between naming tests and other cognitive measures*

	Object names	*Proper names*
WAIS vocabulary	0·72	0·67
Picture Completion	0·45	0·41
Nelson reading	0·73	0·70
Schonell reading	0·69	0·64

	Object name score	*SE*	*Proper name score*	*SE*
Vocabulary score	4·32+(0·38×Obj.)	1·6	7·55+(0·26×Prop)	1·7
Nelson score	−9·55+(1·83×Obj.)	7·4	−2·19+(1·3 ×Prop)	7·7
Schonell score	61·95+(1·40×Obj.)	6·32	74·06+(0·95×Prop)	6·71

these tests and the two naming tests. Thus it is clear that spoken vocabulary, naming vocabulary and reading vocabulary are closely related functions. The nonverbal measure of intelligence, Picture Completion, correlated less highly with the two naming tests. The following regression equations were therefore computed in order to predict WAIS vocabulary scaled scores, Nelson reading scores and Schonell reading scores from scores on the naming tests. The standard error for each regression equation is also given.

The means and standard deviations of the scores on the WAIS subtests, reading tests and naming tests are given in table 2. It must be noted that these measures in the present group of normal subjects are shifted upwards from the scores obtained by the population tested by Wechsler and it is therefore not appropriate to normalise the naming test scores on the same scale, that is with a mean of 10 and standard deviation of 3. Nevertheless, tables for naming scores and their intelligence test equivalents can be derived from the above regression equations (for example see Appendix III).

Subjects

The experimental group consisted of 46 patients with unilateral cerebral lesions of the left hemisphere (established by computed tomography or other radiological investigations). Thirty-two of these patients had well-localised space-occupying lesions and the remaining 14 had vascular lesions considered to be restricted to the left hemisphere. Forty of these patients were referred from the National Hospital for Nervous Diseases, the remaining six from the London and Brook Hospitals. Again, only patients over 18 years of age and educated in this country were included. This group of patients with left hemisphere lesions was tested according to the procedure described for the normal subject in the standardisation of the two naming tests. The control subjects, consisting of 100 normal subjects, are described in the previous section.

Results

Group comparisons

The results of the left hemisphere group and the control group were compared using a *t*-test (see table 2). It is clear that the left hemisphere lesion group is significantly impaired on all these tasks. The question arises as to whether their impairment on the two naming tests merely reflects a generally lowered level of cognitive functioning or whether this group of patients as a whole has nominal deficits independent of their other cognitive deficits. Analysis of covariance[12] partialling out the effects of group differences on WAIS vocabulary, Nelson and Schonell reading scores were computed (table 3). The results showed that the left hemisphere group is significantly poorer in both object and proper naming abilities than the control group even allowing for their impairment in other verbal abilities.

In both the control group and the left hemisphere group the proper names test is significantly harder than the object names test ($t=5·78$, df 99, $p<·001$ and $t=2·91$, df 45, $p<·01$ respectively). A two-way ANOVA on the results of the two naming tests in the two groups confirmed the significant difference in test difficulty ($F=33·1$ df 1,144, $p<·001$) and confirmed the significant difference in group ability

Table 2 *Means and standard deviations for control and left hemisphere lesion subjects on all tests and t-test data for comparison groups*

		Control group (N = 100)	*LH lesion group (N = 46)*	*'t' test (sig level)*
Object names	Mean	22·54	15·15	5·44
	(sd)	(4·3)	(7·15)	(p <0·001)
Proper names	Mean	20·32	13·28	4·48
	(sd)	(5·8)	(7·06)	(p <0·001)
WAIS vocab	Mean	12·83	10·00	3·99
	(sd)	(2·25)	(3·73)	(p <0·001)
Pict com	Mean	11·95	10·07	3·04
	(sd)	(2·39)	(2·65)	(p <0·01)
Nelson	Mean	31·75	22·24	3·14
	(sd)	(10·78)	(14·21)	(p <0·01)
Schonell	Mean	93·57	73·76	4·14
	(sd)	(8·73)	(34·66)	(p <0·001

Table 3 *Comparison of left hemisphere group and controls on the naming tests using analyses of covariance*

Covariate	*Tests*	*(F)*	*Significance*
Vocabulary	Object names	23·9	p <0·001
Vocabulary	Proper names	7·6	p <0·01
Nelson	Object names	33·8	p <0·001
Nelson	Proper names	16·8	p <0·001
Schonell	Object names	21·7	p <0·001
Schonell	Proper names	13·6	p <0·001

($F=54{\cdot}5$, df 1,144, $p<{\cdot}001$). There was no evidence for any difference between left hemisphere and control groups in the pattern of object and proper naming abilities since the groups x test interaction was totally insignificant ($F=0$). The correlation (product moment) between the two naming tests in the control group and in the left hemisphere lesion group was 0·74 and 0·81 respectively. No single patient in the left hemisphere lesion group had an object/proper name discrepancy score exceeding that obtained by any control subject.

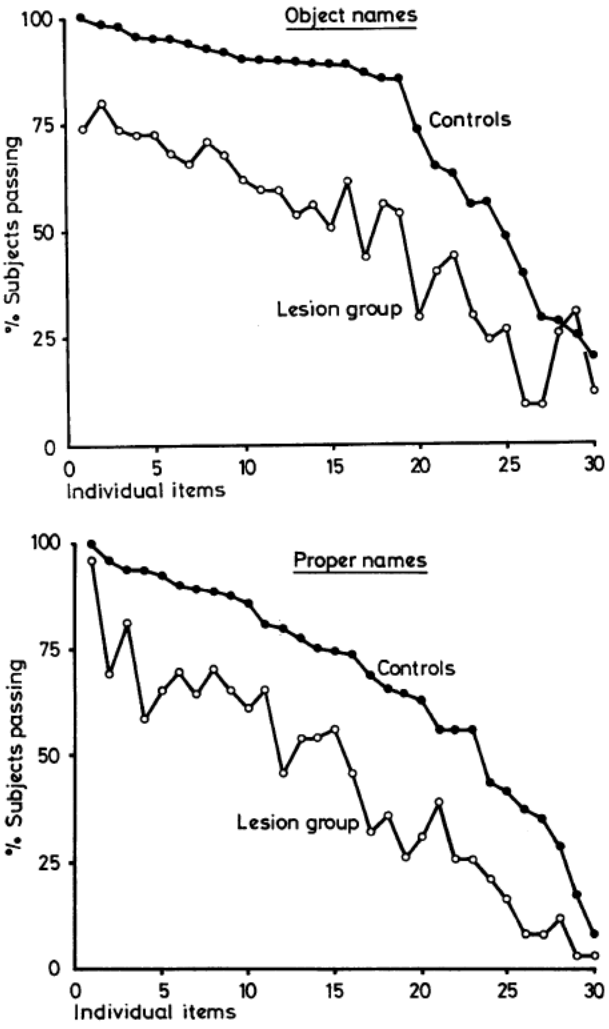

Fig 2 *Percentage of control and left hemisphere subjects passing each item of the Object Names Test and Proper Names Test.*

Item analysis

The 30 items of each naming test were ordered according to item difficulty for the control group and the percentage correct per item for the control group and the left hemisphere lesion group are shown in fig 2. The left hemisphere group scores are parallel with those of the control group but are at a lower level of competence. The finding that these curves appear parallel suggests that there are no qualitative differences between normal and impaired naming skills. For each subject the naming test results were re-analysed to compare performance on the easy (first 15) items and hard (second 15) items and for each naming test a two-way ANOVA was computed (groups x item difficulty). For neither the object names test nor the proper names test was there a significant groups x item difficulty interaction term ($F=140$, df 1,144 NS and $F=0{\cdot}51$, df 1,144, NS respectively), which provides some confirmation that there is no differential effect of item difficulty in the left hemisphere lesion group.

Within hemisphere group comparisons

Since many of the patients in the left hemisphere lesion group did not have a lesion restricted to a single lobe, an inclusive classification was adopted (for example a temporal/parietal lesion case would be allotted to both the temporal and parietal subgroups). However, in order to compare these lesion subgroups with each other, a partially exclusive grouping was adopted, that is the patients with temporal-parietal lesions were excluded from both the temporal and parietal subgroups in computing the significance of the difference between the temporal and parietal subgroups and, similarly, patients with fronto-temporal lesions were excluded from both the temporal and frontal subgroups for the temporal frontal comparison. Thus, for each subgroup comparison the computation is based on two non-overlapping subgroups. This method of analysis has the additional advantage of, to some extent, taking into account a difference in the distribution of size of lesion in each of the three major subgroups. The mean scores and standard deviations for the resulting subgroups are given in table 4 together with the *t*-tests and their significances for the group comparisons. The temporal group is significantly impaired relative to both the parietal and frontal subgroups on the object names test. On the proper names test the temporal subgroups obtained the lowest mean score but the difference between the subgroups does not reach significance.

Discussion

In this paper we have described the construction and standardisation of a graded-difficulty naming test based on a category distinction of object and proper names. The evidence that naming ability is an intelligence-related skill will be discussed and

Table 4 *Comparison of left hemisphere lesion subgroups: mean scores, standard deviations and significance level on the object names and proper names tests*

	Temporals (temp. + temp. frontals) (N = 10)	vs	*Parietals (parietals + front-par.) (N = 8)*		
Object names				*t*	*Significance*
Mean	12·4		17·5		
sd	7·6		7·6	2·60	< 0·02
Proper names					
Mean	11·0		14·6		
sd	6·5		8·2	1·43	N S.
	Temporals (temp. + temp-parietal) (N = 10)	vs	*Frontal (frontals + front-par.) (N = 16)*		
Object names				*t*	*Significance*
Mean	10·6		16·7		
sd	6·9		5·6	4·16	< 0·001
Proper names					
Mean	10·9		13·5		
sd	6·0		7·0	1·68	N.S.

the relevance of this relationship for clinical assessment will be considered.

It was shown that performance on the naming tests correlates highly in normal subjects with spoken vocabulary as measured by the standard vocabulary subtest of the WAIS and with reading vocabulary as measured by the Schonell and Nelson. Furthermore these three tests are generally accepted as robust indices of general intelligence level in normal subjects. The implications of these findings in the clinical context are obvious—in testing for nominal dysphasia it must be helpful to obtain a measure of an individual's present level of functioning on an ordinal scale. This can now be achieved by using a test of graded difficulty. To date, the identification of a minimal or even a mild degree of nominal dysphasia is largely a matter of clinical judgement. However, the present test enables a predicted score on the reading and vocabulary tests to be computed from the score obtained on the naming test. Thus a naming score is converted to a percentile measure, for example for any naming score an equivalent vocabulary scaled score can be computed from the regression equation. This value can be accepted as an indication of the patient's present nominal abilities which can then be compared with other test scores and with a clinical estimate of the patient's premorbid intelligence.

It is hoped that in mild cases of nominal dysphasia a quantitative measure may be illuminating and that in more severe cases of nominal dysphasia where the deficit is obvious a quantitative statement may add to the value of a case description. In addition these naming tests provide a tool for monitoring improvement or deterioration of this language skill in any individual patient.

It has previously been reported by Weisenburg and McBride,[13] Rochford and Williams[3] and Newcombe *et al*[2] that high frequency names are less vulnerable to word finding difficulties than are low frequency names. The present results confirm these findings. The performance of the left hemisphere lesion group was depressed but qualitatively similar to that of the control group. There was no differential effect in the left hemisphere group of task difficulty. This was an expected finding which supports the generally accepted view that low frequency items are especially vulnerable to nominal difficulties and reinforces the clinical necessity of a naming test which is graded in difficulty.

Comparison of performance on the object and proper names provided little or no evidence of category specificity in the left hemisphere lesion group as a whole. The groups x tests interaction was totally insignificant and indeed in no single case was there a striking impairment or preservation of object or proper names. The single case study reported in Appendix I, considered in the perspective of these group data, highlights the rarity of the incidence of highly circumscribed and selective deficits in a neurological population. This patient was shown to have a very small lesion due to a minor stroke from which she recovered rapidly. It should be noted that the majority of subjects of this study had larger and more incapacitating lesions.

Finally, as our population were not chosen on the criterion of the presence of aphasia, consideration of the anatomical correlates of nominal dysphasia becomes viable. A number of previous studies have emphasised the association of temporal lobe lesions and nominal dysphasia.[14] Coughlan and Warrington[15] found that although nominal skills were impaired in all lesion groups, the temporal lobe group was significantly more impaired than either the frontal or the parietal lesion groups. The present study replicates this finding and we conclude that although

an integrity of many areas of the left hemisphere is necessary for intact naming skills, word retrieval processes are subserved in the main by structures in the left temporal lobe. It is possible that failure to take into account the problem of task difficulty has led to the opposite view that nominal problems have little or no localising significance.[16 17]

APPENDIX 1

A single case study of a category-specific naming deficit for names of people. Case report

GBL (Hospital No. A81818), a 55 year old secondary school teacher was admitted to the National Hospital in May 1975 for investigation of intermittent visual disturbances and poor memory. On examination she was found to have a right upper quadrantic field defect. There were no other neurological signs and in particular her language functions appeared normal. Gamma scan was normal but computed tomography showed a small infarct in the region of the posterior temporal branch of the middle cerebral artery of the left hemisphere (fig 3).

Psychological findings GBL was tested on the WAIS and obtained a verbal IQ of 130 and a performance IQ of 116. On a recognition test (2 choice) for written words she scored 44/50 which is within the average range (scaled score 10)* and on a comparable memory test for faces she scored 48/50 which is within the superior range (scaled score 15)*. Her reading and spelling were entirely normal. On routine testing verbal comprehension, object naming and verbal fluency appeared entirely normal. On the Oldfield naming test she responded quickly and scored 26/26 correct. In contrast on a test of naming well-known personalities her performance was quite impaired: she named only three out of 20 photographs (scaled score 3)* in spite of having no difficulty in identifying all but two of them by description. (For example, when shown a photograph of Mr Heath, she responded "Conservative, was Prime Minister, organist, comes from the South Coast".) This apparently selective and circumscribed difficulty in identifying people by name was investigated further.

GBL was asked to name the author of 20 well-known books all of which she had read, for example "Who wrote Pride and Prejudice?"; she scored 7/20. Similarly, she was asked to name from their description 20 political and national leaders. She claimed knowledge of all these personalities but she was only able to name nine of them correctly. She did not appear to have comparable difficulty in naming places (towns) on a map. She succeeded in identifying 16 of 20 European towns and 12 of 12 English towns.

Her ability to generate proper names from specific categories appeared to parallel her naming difficulties. She was able to produce 22 town names in 60 seconds but only two political or national leaders and only three English prime ministers in the same time limit. She did rather better with authors, producing nine in the 60 seconds. However, when names of specific people were not required, her performance was very much better; she generated 19 girls names and 14 surnames in separate 60 second periods.

We argue from these results that GBL has a nominal deficit affecting one particular class of proper nouns, (names of people) whilst another class of proper nouns, (names of towns), was spared. Whether naming was from a visual representation or from a verbal description did not appear to affect the severity of the deficit. In conclusion we suggest that GBL provides a further example of a category-specific naming deficit.

*Normalised scores Mean 10, SD 3, Warrington, unpublished.

APPENDIX II

Objects	*Proper names*
1 Kangaroo	1 Hitler
2 Scarecrow	2 Eiffel Tower
3 Buoy	3 Henry VIII
4 Thimble	4 Italy
5 Handcuffs	5 Queen Victoria
6 Tweezers	6 Napoleon
7 Corkscrew	7 Mona Lisa
8 Sporran	8 Ghandi
9 Tassel	9 Joan of Arc
10 Sundial	10 Eros
11 Chopsticks	11 L Armstrong
12 Periscope	12 Lawrence of Arabia
13 Boar	13 S America
14 Blinkers	14 Taj Mahal

Objects

15 Monocle
16 Turtle
17 Trampoline
18 Bellows
19 Shuttlecock
20 Anteater
21 Pagoda
22 Radius
23 Leotard
24 Mitre
25 Yashmak
26 Sextant
27 Centaur
28 Cowl
29 Tutu
30 Retort

Proper names

15 Elizabeth I
16 F Nightingale
17 Mao Tse Tung
18 Shakespeare
19 Castro
20 Canute
21 Harold
22 Kremlin
23 Lincoln
24 Lenin
25 Rasputin
26 Trotsky
27 Parthenon
28 Disraeli
29 Marx
30 Virginia Woolf

APPENDIX III

Prediction of vocabulary from naming scores

Objects (vocab = 4·32 + (0·38 × object)

Objs	*Vocab*
30	16
29	
28	15
27	
26	
25	14
24	
23	13
22	
21	
20	12
19	
18	
17	11
16	
15	10
14	
13	
12	9
11	
10	
9	8
8	
7	7
6	
5	
4	6
3	
2	5
1	
0	4

Proper (vocab = 7·55 + (0·26 × proper)

Proper	*Vocab*
30	
29	15
28	
27	
26	
25	14
24	
23	
22	
21	13
20	
19	
18	12
17	
16	
15	
14	11
13	
12	
11	
10	
9	10
8	
7	
6	9
5	
4	
3	
2	8
1	
0	

We thank the physicians and surgeons of the National Hospital for Nervous Diseases and the Brook Hospital for permission to test patients under their care. We are grateful to Professor RW Gilliatt for permission to study GBL and to report our findings. We wish to thank Dr Alan M Whiteley who prepared the brain diagram. We are also grateful to Dr RTC Pratt and Dr T Shallice for their helpful comments in the preparation of this manuscript. We would particularly like to thank Dr Hazel Nelson for her invaluable advice in this investigation.

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Psychological Medicine, 1997, **27**, 967–971.

BRIEF COMMUNICATION

Performance on the delayed word recall test (DWR) fails to differentiate clearly between depression and Alzheimer's disease in the elderly

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ABSTRACT

Background. The differential diagnosis of early dementia of the Alzheimer's type from depression in the elderly is often made difficult by the presence of significant memory impairment in depressed patients. The Delayed Word Recall test (DWR) was developed to facilitate the early diagnosis of Alzheimer's disease. The DWR involves: (*a*) repeated elaborate encoding of ten separate words; (*b*) a filled delay; (*c*) delayed free recall. A recognition memory test has also been recently developed. The available evidence suggests impressive sensitivity and specificity when the DWR has been used to separate patients with early Alzheimer's disease from very well matched controls.

Methods. In the present study, the DWR was evaluated with regard to its ability to separate a group of 50 patients with early Alzheimer's disease from 50 elderly patients with major depression in a between-subjects experimental design.

Results. For both free recall and recognition indices, the between-group overlap was large. Using recommended cut-off scores for the detection of Alzheimer's disease, 44% of the depressed patients would have been misclassified as demented based on their free recall scores, and 48% of the depressed patients would have been misclassified on the basis of their recognition scores.

Conclusion. We conclude that the DWR is not specific enough to clearly distinguish patients with early Alzheimer's disease from elderly patients with major depression.

INTRODUCTION

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Original Research Article

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and Geriatric
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Early Detection and Differential Diagnosis of Alzheimer's Disease and Depression with Neuropsychological Tasks

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Key Words

Early detection · Alzheimer's disease · Depression · Neuropsychological assessment · Differential diagnosis · Neural and pharmacotherapeutic implications

Abstract

The development of novel treatments for Alzheimer's disease (AD), aimed at ameliorating symptoms and modifying disease processes, increases the need for early diagnosis. Neuropsychological deficits such as poor episodic memory are a consistent feature of early-in-the-course AD, but they overlap with the cognitive impairments in other disorders such as depression, making differential diagnosis difficult. Computerised and traditional tests of memory, attention and executive function were given to four subject groups: mild AD (n = 26); questionable dementia (QD; n = 43); major depression (n = 37) and healthy controls (n = 39). A visuo-spatial associative learning test accurately distinguished AD from depressed/control subjects and revealed an apparent subgroup of QD patients who performed like AD patients. QD patients' performance correlated with the degree of subsequent global cognitive decline. Elements of contextual and cued recall may account for the task's sensitivity and specificity for AD.

Introduction

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11. DEVICE DESCRIPTION

Product Name: Cantab Mobile
Indication: Assess Memory in Patients Aged 50 to 90 Years

Sponsor

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1 DEVICE DESCRIPTION

Cantab Mobile is software to be loaded and run on Apple iPad hardware and operating system (Figure 1). Below is a list of possible device accessories:

- The iPad[1] is an essential accessory
- Disposable iPad Sleeve (see also **Instructions for Use [Section 13]**) for cleaning recommendations)
- iPad stand
- A iPad battery charger is also supplied with the iPad

Figure 1. iPad with App Icon at Top Left

Cantab Mobile does not have a restricted shelf-life. Ongoing support of the manufacturer is required, however, and is detailed below.

The medical device software must be updated when new releases are made available. The iPad operating system should also be kept up to date. Both may be achieved automatically. The iPad battery should be charged as required. No calibration is necessary.

Ongoing support by the manufacturer is required. The app must be able to confirm periodically with the manufacturer that it is licensed, and be updated as required over time.

1 Cantab Mobile is not authorized for use on the iPad mini or the iPad 1 (the first generation iPad). Do not install the app on these devices.

The test is not susceptible to environmental influences within the defined environment for its administration. We instruct that physicians must always administer the tests in a quiet, peaceful environment, with the iPad volume level set so that the patient can clearly hear instructions being given. For patients with impaired hearing, additional support may need to be provided to ensure they can correctly hear and understand the instructions during the test, e.g. use headphones.

A technical wireframe, or mobile app screen blueprint, of Cantab Mobile is a supportive document that presents the skeletal framework, interface elements, and navigational flow (See Cantab Mobile Wireframes).

1.1 Patient Data Entry

Prior to the PAL test itself, the healthcare professional administering the test enters patient data (patient ID, date of birth, gender, educational background etc.).[2] This is used in assessing the patient's performance against a set of normative data.

Figure 2. Data Entry Screen

1.2 Memory Test

Cantab Mobile provides an optional patient self assessment of memory (Self Assess - enabled on the data entry screen). If this assessment is enabled, the patient will rate his/her memory prior to taking Cantab PAL. The patient is presented a rating scale against which they rate their memory as above average (left of center), average (center), or below average (right of center) (See Appendix A). Comparing self-rated memory with the objective

2 Patient details must be entered correctly. Incorrect patient details can lead to incorrect reporting of patient impairment.

measure of memory, provided by Cantab PAL, can reveal any discrepancies between actual and perceived memory ability.

The Cantab Mobile memory test is based on the Cantab PAL test previously used on other hardware platforms. The Cantab PAL requires patients to learn and remember abstract visual patterns associated with various locations on a touch-sensitive computer screen. The patterns were all created to be bold, brightly colored, abstract and with no cultural context
See Appendix B for examples of patterns used.

Patterns are presented in six boxes around the edge of the screen (See Figure 3). The patterns disappear from the screen, leaving empty boxes and, after a brief delay, the same patterns are presented sequentially in the middle of the screen and the patient is required to touch the box in which they previously saw that pattern appear. (Figure 4)

Figure 3. Pattern Appears in Box

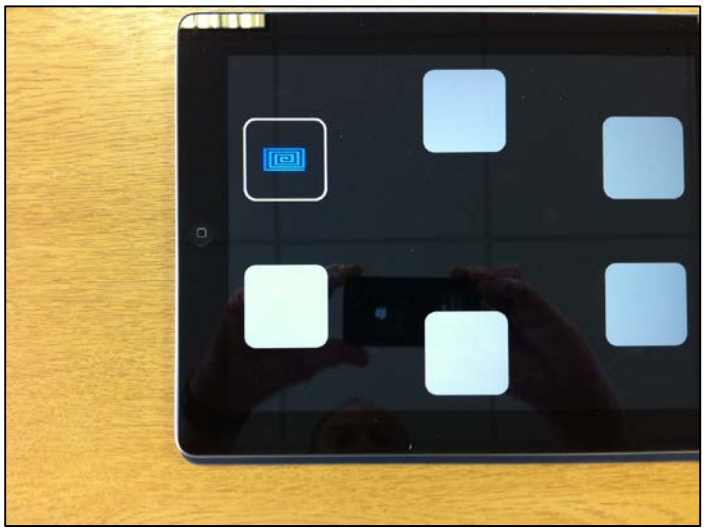
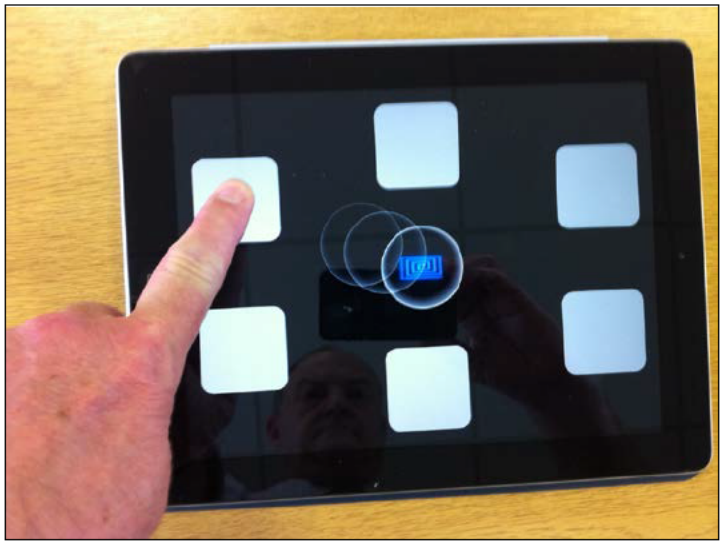


Figure 4. Patient Chooses Box



If the patterns' locations are not recalled correctly, this is identified to the patient via audio prompts and pattern presentation and recall is repeated. This process continues until the task is completed successfully, at which point the next task is started, or repeated failures by the patient to recall the locations correctly cause the test to end. The whole test consists of a series of such tasks with increasing levels of difficulty.

The patient's responses are recorded by screen touches. The number of errors that they make are recorded and their performance is graded using algorithms derived from a normative database (b) (4)

1.3 Questionnaire(s)

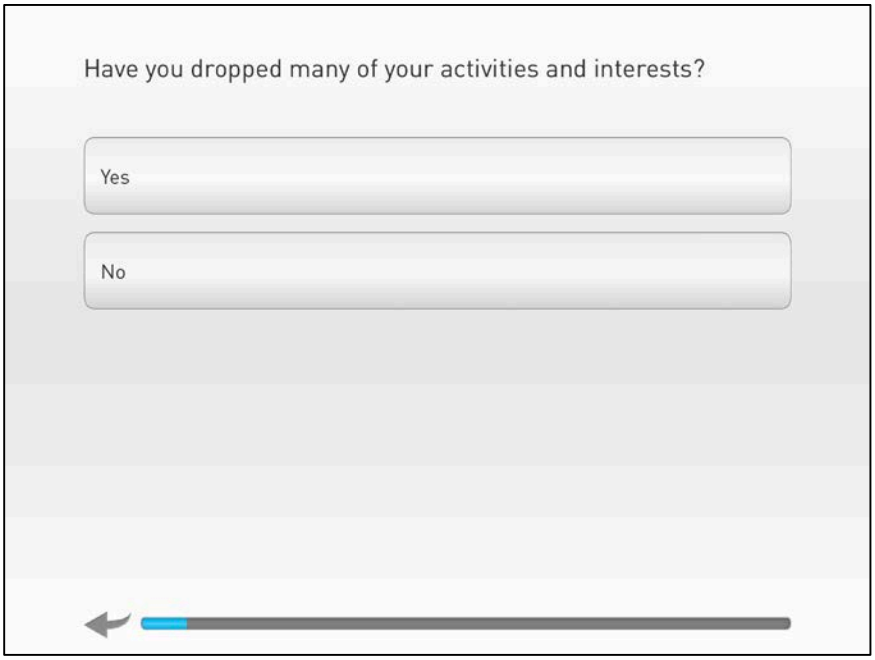
Cantab Mobile additionally includes optional questionnaires. Questionnaires operate by presenting a series of questions to the patient, with clearly labeled response boxes that the patient may touch in order to answer each question (Figure 5). Ratings scales administered (depending on patient performance, and if not disabled by the healthcare professional) comprise:

1. GDS – Geriatric Depression Screening Questionnaire (See Appendix C)
2. ADL – Activities for Daily Living Questionnaire (See Appendix D)

The GDS rating scale in the app is the shorter version of GDS including 15 questions, the GDS-15 (Almeida and Almeida 1999), which is based on the GDS described by Yesavage and colleagues (Yesavage et al 1983): The GDS rating scale comprises a series of questions, each presented in turn textually on the screen using the language in force, two buttons below to allow the patient to respond 'yes' and 'no' (or equivalent in the language in force). A progress bar gives an approximate indication of progress through the questions and

a button with a backward arrow allows the user to return to the preceding question (if any) and choose again. See Figure 5 below for an example of a GDS-15 rating scale question and its format, as it is presented in the app.

Figure 5. GDS Rating Scale and Format

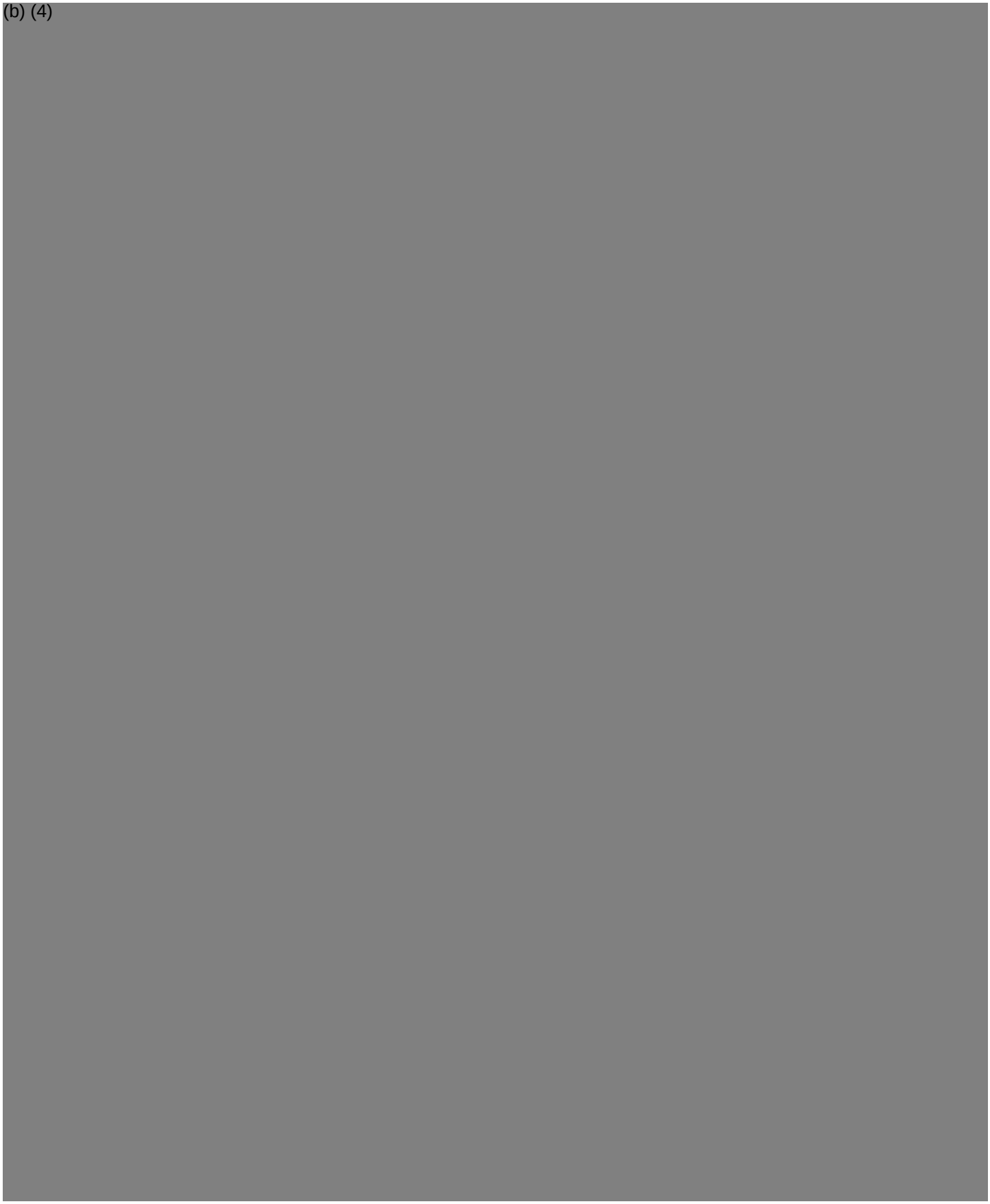


Administration of the ADL rating scale comprises a series of questions, each presented in turn textually on the screen using the language in force[3], with the introductory text given above the question and buttons below to allow the patient to choose from the responses permitted for the question. A progress bar gives an approximate indication of progress through the questions and a button with a backward arrow allows (except on questions 1 and 11) the user to return to the preceding question and choose again.

(b) (4)

3 The entire user interface respects the text direction (left-to-right or right-to-left) of the language in force including the backward arrow button and progress bar

(b) (4)



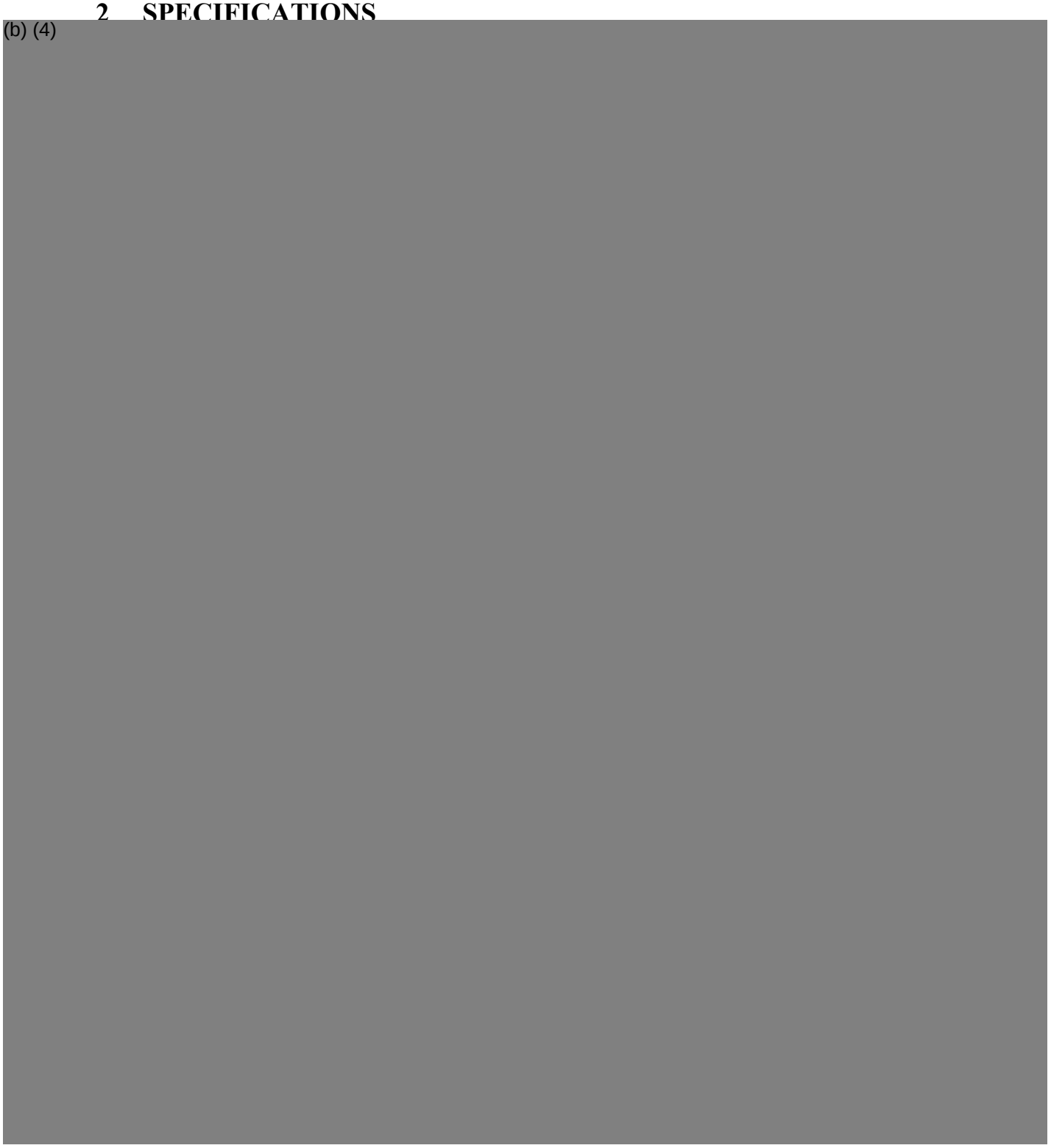
(b) (4)

1.5 Device Classification

The device is presently classified IIa under EU directive 93/42/EEC. It is standalone software that could be regarded as allowing monitoring of vital physiological processes (MEDDEV 2.1/6 section 3.1.1).

2 SPECIFICATIONS

(b) (4)



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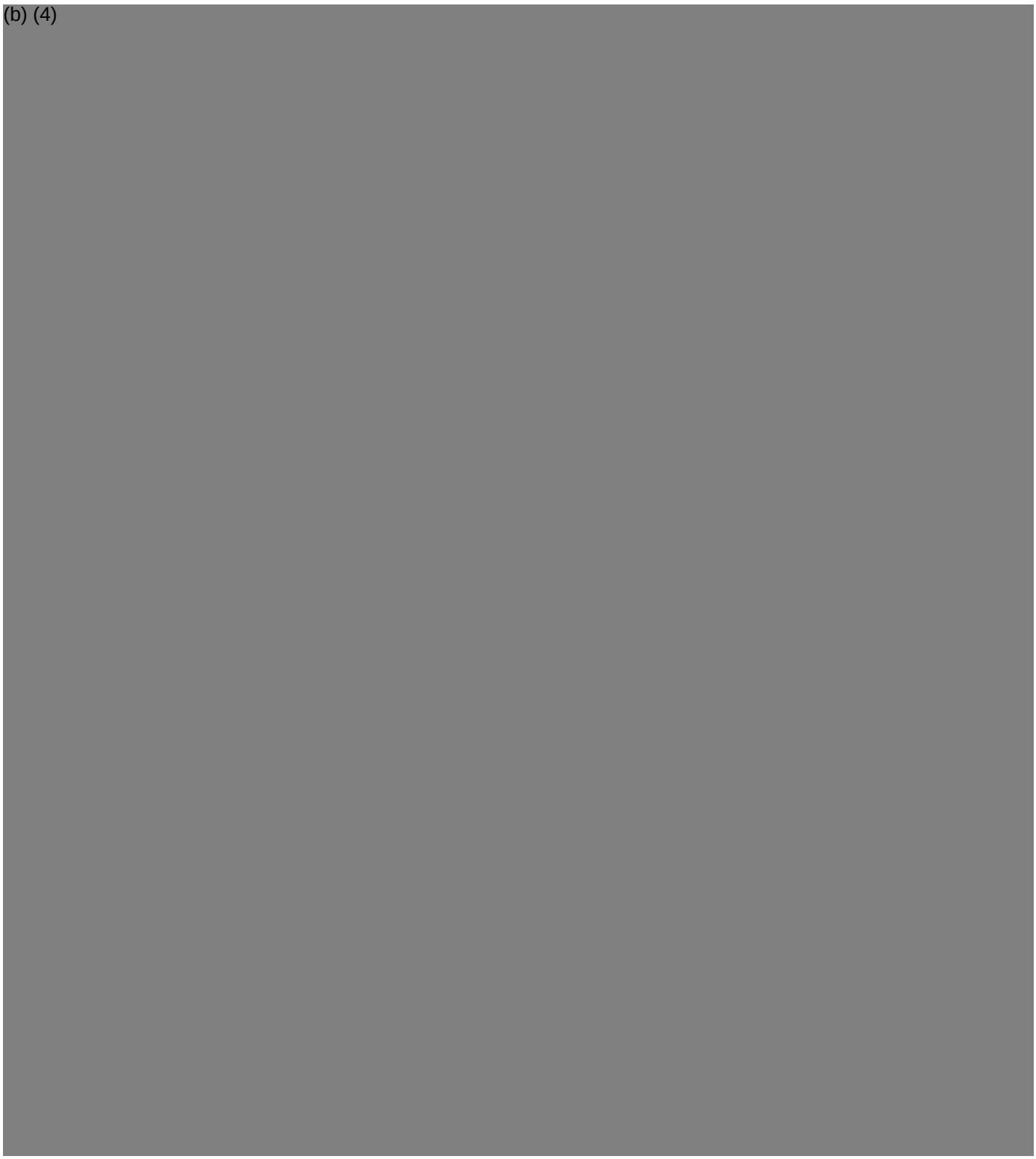

2.2 Device Safety Characteristics and Risks

Risk management for the device is handled under controlled procedures within a Quality Management System. These procedures are designed to meet applicable requirements of EN ISO 13485:2012 and EN ISO 14971:2012.

Identification of characteristics of the device that could impact on safety are documented in **QRM-01-001**. Risk analysis was conducted according to a risk analysis plan referencing controlled procedures, namely **QRM-02-002**, and the conclusion of the risk analysis process is documented in report **QRM-02-003**.

The summary of all points of the risk analysis is provided in **QRM-02-001**.

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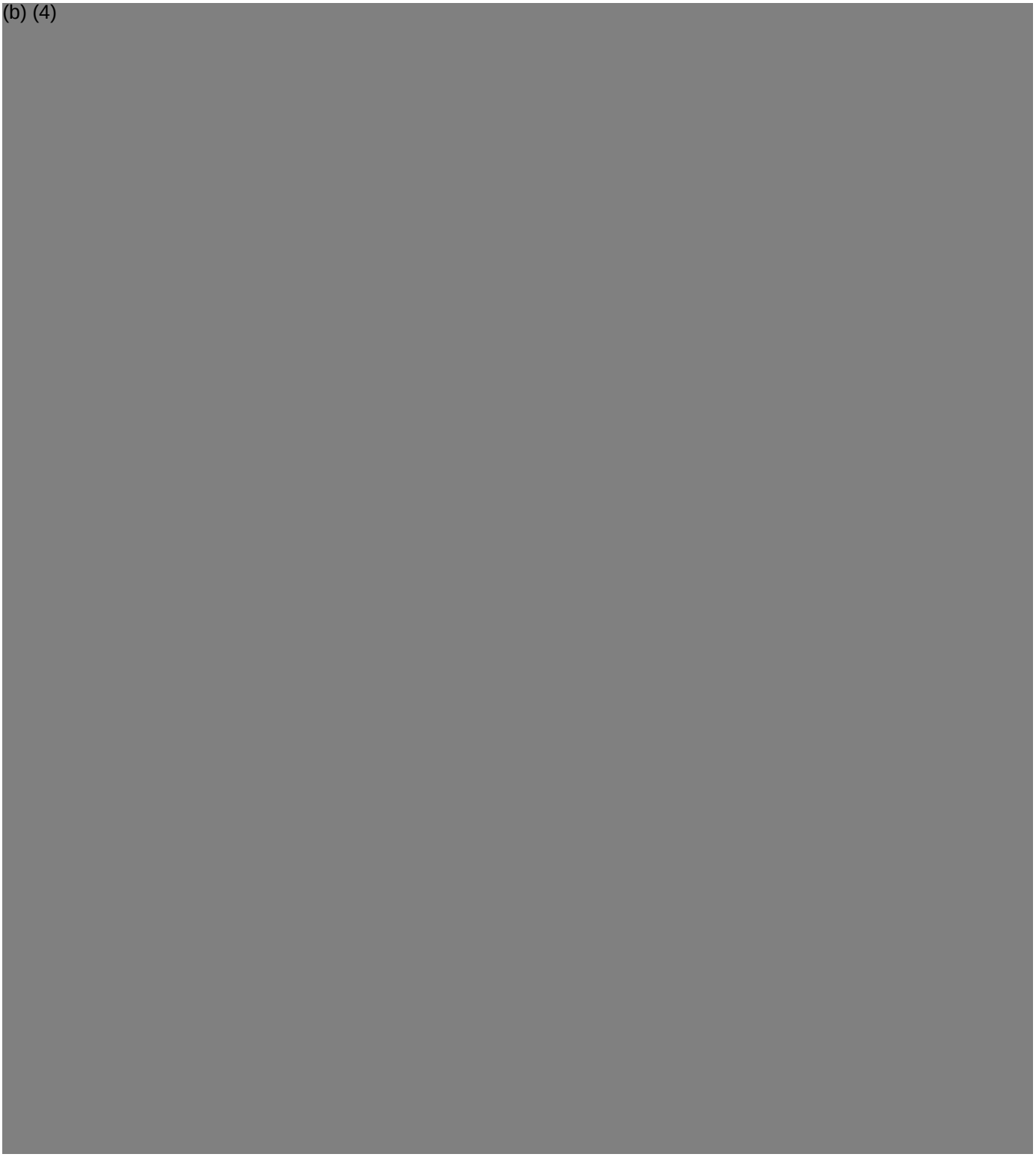
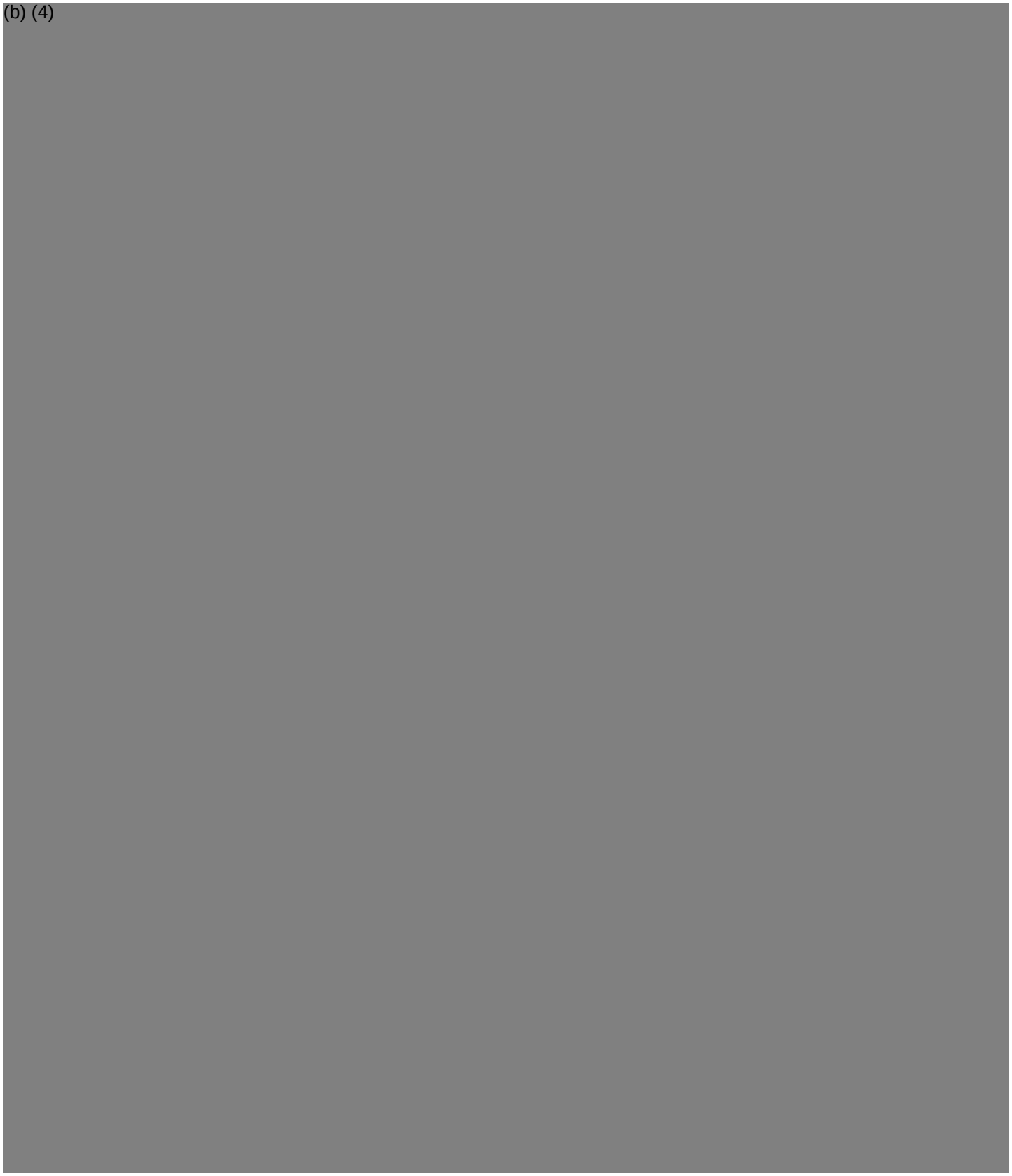
4 APPENDICES

(b) (4)



(b) (4)



Appendix C. Mood Assessment (GDS)

The Mood Assessment (GDS) is automatically administered. Cantab PAL performance is not a conditional factor in administering the Mood Assessment.

Are you basically satisfied with your life?
☐ Yes
☐ No

Have you dropped many of your activities and interests?
☐ Yes
☐ No

Do you feel that your life is empty?
☐ Yes
☐ No

Do you often get bored?
☐ Yes
☐ No

Are you in good spirits most of the time?
☐ Yes
☐ No

Are you afraid that something bad is going to happen to you?
☐ Yes
☐ No

Do you feel happy most of the time?
☐ Yes
☐ No

Do you often feel helpless?
☐ Yes
☐ No

Do you prefer to stay at home, rather than going out and doing new things?
☐ Yes
☐ No

Do you feel you have more problems with memory than most?

☐ Yes

☐ No

Do you think it is wonderful to be alive now?

☐ Yes

☐ No

Do you feel pretty worthless the way you are now?

☐ Yes

☐ No

Do you feel full of energy?

☐ Yes

☐ No

Do you feel that your situation is hopeless?

☐ Yes

☐ No

Do you think that most people are better off than you are?

☐ Yes

☐ No

Appendix D. Functional Assessment (ADL)

This test is automatically administered after Cantab PAL if the patient's Cantab PAL performance has indicated that they fall in the "Investigate" category

Part 1:

In the past 3 months, were you able to:

Do your own shopping?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Prepare meals?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Write checks, pay bills, or use an ATM case machine?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Travel by car or public transport?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Carry out housework, laundry or home repairs?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Do hobbies such as a card games or crosswords?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Follow the story of a TV program, book or movie?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Keep track of current events in the news or the media?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Remember appointments or important dates such as birthdays?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Remember to take your medication?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Part 2:

Can you:

See well enough to recognize someone across the street (wearing glasses or contact lenses if necessary?)

☐ Yes
☐ No

Hear what people are saying when they are speaking at a normal volume?

☐ Yes
☐ No

Walk up and down a set of stairs without help?

☐ Yes
☐ No

(b) (4) Device Description

(b) (4) Device Description

(b) (4) Device Description

5 REFERENCED DOCUMENTS

Cantab Mobile Technical Wireframes

Cantab Mobile Managing Reports Quick Reference Guide

Demographic Adjustment of Scores (NMI-020)

Identification of Characteristics (QRM-01-001)

PALD Risk Management Plan (QRM-02-002)

Risk Summary Report (QRM-02-003)

Risk Analysis (QRM-02-001)

(b)(4)

(b)(4)

(b) (4)

(b)(4)

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(b)

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Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the document is approved for use.

Management Approval : Owner			
Name:	Ian Cartland	Role:	Project Manager
Signature:		Date:	

Management Approval : Additional			
Name:	Jenny Barnett	Role:	Requirements Representative (Science)
Signature:		Date:	

Approval by the Quality Manager (QA), indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the document is approved for use.

Quality Assurance Approval			
Name:	Ricky Dolphin	Role:	Nominated Delegate Quality Manager
Signature:		Date:	

Document History

Version	Date released for approval	Developer Initials	Reviewer Initials	Changes from Previous Version
4.0	29 May 2015	IC	JB	Revisions for multi-domain mode and from review. Updated document template.

Guidelines on Identifying Medical Device Characteristics that could Impact on Safety
Extracted from EN ISO 14971:2012 Annex C

C1. General

Sub clause 4.2 requires that the manufacturer identify those characteristics of the medical device that could affect safety. Consideration of these characteristics is an essential step in identifying the hazards of the medical device as required in 4.3. One way of doing this is to ask a series of questions concerning the manufacture, intended users, intended use, reasonably foreseeable misuse, and ultimate disposal of the medical device. If one asks these questions from the point of view of all the individuals involved (e.g., users, maintainers, patients, etc.), a more complete picture can emerge of where the hazards can be found. The following questions can aid the reader in identifying all the characteristics of the medical device that could affect safety.

The list is not exhaustive, or representative of all medical devices, and the reader is advised to add questions that can have applicability to the particular medical device and to skip questions that are not relevant to the particular medical device. The reader is also advised to consider each question not only on its own but also in relation to others.

Hazard ID No	C.2 Questions	Applicable Y/N
1	**C.2.1: What is the intended use and how is the medical device to be used?** The medical device is designed to detect episodic memory impairments in patients aged 50-90 who may be experiencing mild cognitive impairment (MCI) or dementia. Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living. The device is used by the patient, under supervision by medical staff. The patient simply follows the audio instructions produced by the device, touching the screen to provide their answers when prompted. **Cantab Mobile is not a diagnostic test.** A diagnosis can only be made by a qualified physician using consensus diagnostic criteria.	**Yes**
2	**C.2.2: Is the medical device intended to be implanted?**	**No**
3	**C.2.3: Is the medical device intended to be in contact with the patient or other persons?** Only the third-party hardware on which the medical device software runs is in contact with the patient.	**No**
4	**C.2.4: What materials or components are utilized in the medical device or are used with, or are in contact with, the medical device?** None	**No**

Hazard ID No	C.2 Questions	Applicable Y/N
5	**C.2.5: Is energy delivered to or extracted from the patient?**	No
6	**C.2.6: Are substances delivered to or extracted from the patient?**	No
7	**C.2.7: Are biological materials processed by the medical device for subsequent re-use, transfusion or transplantation?**	No
8	**C.2.8: Is the medical device supplied sterile or intended to be sterilized by the user, or are other microbiological controls applicable?**	No
9	**C.2.9: Is the medical device intended to be routinely cleaned and disinfected by the user?**	No
10	**C.2.10: Is the medical device intended to modify the patient environment?**	No
11	**C.2.11: Are measurements taken?** The device does not have a measuring function in the sense of Annex VII paragraph 5 of MDD and MEDDEV 2.1/5. The patient's responses (screen touches) are logged in order to calculate test scores. The patient's test scores are compared with algorithms derived from a normative database of at least several hundred individuals collected during academic research in the UK, which takes into account their age, gender and level of education.	Yes
12	**C.2.12: Is the medical device interpretive?** The medical device is interpretive. The output provided by the device is not diagnostic. A diagnosis can only be made by a qualified physician using consensus diagnostic criteria.	Yes
13	**C.2.13: Is the medical device intended for use in conjunction with other medical devices, medicines or other medical technologies?**	No
14	**C.2.14: Are there unwanted outputs of energy or substances?**	No
15	**C.2.15: Is the medical device susceptible to environmental influences?** The test is not susceptible to environmental influences within the defined environment for its administration.	No

Hazard ID No	C.2 Questions	Applicable Y/N
16	**C.2.16: Does the medical device influence the environment?**	No
17	**C.2.17: Are there essential consumables or accessories associated with the medical device?** The iPad is an essential accessory and, if needed, headphones. In the interests of hygiene we also recommend wiping the touch screen of the iPad with a standard alcohol disinfectant disposable wipe between each patients use. Alternatively a disposable iPad sleeve may be employed and discarded after each use.	Yes
18	**C.2.18: Is maintenance or calibration necessary?** The medical device software must be updated when new releases are made available. The iPad operating system should also be kept up to date. Both may be achieved automatically. The iPad battery should be charged as required. No calibration is necessary.	Yes
19	**C2.19: Does the medical device contain software?** The medical device is stand-alone software.	Yes
20	**C.2.20: Does the medical device have a restricted shelf life?**	No
21	**C.2.21: Are there any delayed or long-term use effects?**	No
22	**C.2.22: To what mechanical forces will the medical device be subjected?** None directly as it is stand-alone software.	No
23	**C.2.23: What determines the lifetime of the medical device?** Ongoing support by the manufacturer is required. The app must be able to confirm periodically with the manufacturer that it is licensed, and be updated as required over time.	Yes
24	**C.2.24: Is the medical device intended for single use?**	No
25	**C.2.25: Is safe decommissioning or disposal of the medical device necessary?**	No
26	**C.2.26: Does installation or use of the medical device require special training or special skills?** Installation and operation are straightforward, using a standard mobile device touch interface. The Instructions for Use (IFU) clearly and fully describe correct operation for both the physician and the patient.	No

Hazard ID No	C.2 Questions	Applicable Y/N
27	**C.2.27: How will information for safe use be provided?** All required information is contained within the IFU.	Yes
28	**C.2.28: Will new manufacturing processes need to be established or introduced?**	No
29	**C.2.29: Is successful application of the medical device critically dependent on human factors such as the user interface?**	See sub-items below
29.1	**C.2.29.1: Can the user interface design features contribute to use error?** Patient details must be entered correctly. Incorrect patient details can lead to incorrect reporting of patient impairment.	Yes
29.2	**C.2.29.2: Is the medical device used in an environment where distractions can cause use error?** The test is not susceptible to environmental influences within the defined environment for its administration. We instruct that physicians must always administer the tests in a quiet, peaceful environment, with the iPad volume level set so that the patient can clearly hear instructions being given. For patients with impaired hearing, additional support may need to be provided to ensure they can correctly hear and understand the instructions during the test, e.g. use headphones.	No
29.3	**C.2.29.3: Does the medical device have connecting parts or accessories?** The only required accessory is the iPad itself (see.C.2.17). A charger is also supplied with the iPad and required for use only between patient testing sessions.	Yes
29.4	**C.2.29.4: Does the medical device have a control interface?** The control interface is basic and is not accessed by the patient. It is accessed by the physician to synchronise the device and enable or disable test options.	Yes
29.5	**C.2.29.5: Does the medical device display information?** The patient simply follows the instructions that they hear and touch the screen to provide their answers in response to the test stimuli presented.	Yes
29.6	**C.2.29.6: Is the medical device controlled by a menu?** The control interface is basic and is not accessed by the patient. It is accessed by the physician to synchronise the device and enable or disable test options.	Yes

Hazard ID No	C.2 Questions	Applicable Y/N
29.7	**C.2.29.7: Will the medical device be used by persons with special needs?** Cantab Mobile is not suitable for individuals with severe visual impairment or those outside the indicated age range. The option to test or not to test is a decision that rests with the medical professional. Testing is supervised by a medical professional. A substantial number of peer reviewed publications describe the use of PAL in patients with cognitive impairment, and of the other tests included in Cantab Mobile in relevant populations.	Yes
29.8	**C.2.29.8: Can the user interface be used to initiate user actions?** See C.2.29.1.	Yes
30	**C.2.30: Does the medical device use an alarm system?**	No
31	**C.2.31: In what way(s) might the medical device be deliberately misused?** Maintenance may be neglected. Instructions may not be followed correctly, e.g. entry of incorrect patient data.	Yes
32	**C.2.32: Does the medical device hold data critical to patient care?** Temporarily, the device holds patient report data prior to its transfer to the primary care provider's systems.	Yes
33	**C.2.33: Is the medical device intended to be mobile or portable?** The medical device is software intended to run on a mobile device.	Yes
34	**C.2.34: Does the use of the medical device depend on essential performance?**	No

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the document is approved for use.

Management Approval : Owner			
Name:	Ian Cartland	Role:	Project Manager
Signature:		Date:	

Approval by the Quality Manager (QA) indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the document is approved for use.

Quality Assurance Approval			
Name:	Ricky Dolphin	Role:	Nominated Delegate Quality Manager
Signature:		Date:	

Document History

Version	Date released for approval	Developer Initials	Reviewer Initials	Changes from Previous Version
1.0	15/Jul/2011	High Edge	HHR	New Document
2.0	14/Jun/2015	IC	RD	Updated year of referenced regulations. Corrected description for multi-domain mode.

cambridge cognition

Cantab Mobile

1. Purpose and scope

This Risk Management Plan describes the activities undertaken to assess the risks associated with **Cantab Mobile** This plan complies with the requirements of EN ISO 14971:2012 Medical Devices – Application of risk management to medical devices.

2. Introduction

Cantab Mobile is medical device software, for assessment of cognition in a healthcare environment. Refer to PTF-001-001 for an overview of the device.

3. Risk Management Plan

This Risk Management Plan has been developed in accordance with the requirements of EN ISO 14971:2012, **SOP QRM-01, Risk Management File** and **SOP QRM-02, Risk Management Process**.

The plan is divided into two phases:

i) Description of the intended use of the device and identification of the characteristics that could affect the safety of the device to patients, carers and the environment. Annex C of EN ISO 14971:2012 will be used to identify the device characteristics that could impact on safety.

ii) Identification of known or foreseeable hazards using as a guide, Annex E of EN ISO 14971:2012. For each hazard identified, its risk potential will be estimated based on the severity and occurrence likelihood identified in this plan and **SOP QRM-02, Risk Management Process** and the actions taken to reduce the risk(s) identified.

On completion of the above analyses the Project Manager will review the actions to ensure that the risk control measures are appropriate for reducing the risk(s) to an acceptable level. If any residual risk has a 'high' level of concern, the Project Manager will ensure that the medical benefits of the device outweigh the residual risks. A Risk Summary Report will be prepared and added to the Risk Management File.

4. Responsibilities

The Project Manager is responsible for:

- Ensuring a Risk Management File is prepared for each project undertaken by the company;
- Assembling a Risk Management Team for the project with inputs from personnel having the appropriate knowledge and skills.

The Quality Manager has overall responsibility for the Risk Management Process.

The Risk Management Team will consist of, as a minimum, the Project Manager and the Quality Manager.

5. Risk estimation

The occurrence of the hazard shall be evaluated according to the following:

Occurrence of the Hazard		
Ranking	**Selection**	**Meaning**
1	Remote	So unlikely, occurrence is not expected
2	Rare	Unlikely. Feasible but unlikely in common use
3	Occasional	Shall occur relatively infrequently. May occur under certain conditions
4	Frequent	Can expect to occur with some regularity. Testing shows occurrence is predictable.
5	Continuously occurring	Shall occur on a regular basis. Known performance litigation.

The severity of the harm shall be evaluated according to the following and estimated based on the most likely type of injury to the end user.

Severity of the harm		
Ranking	**Selection**	**Meaning**
1	None	No adverse health consequence. Could cause minor nuisance or inconvenience to end user
2	Limited	Transient, self limiting illness or injury. Could cause temporary discomfort.
3	Moderate	Significant impairment, but temporary/reversible
4	Severe	Serious injury, permanent impairment, irreversible.
5	Life threat	Life threatening, death could occur

The risk shall be evaluated using the following table:

OCCURRENCE	SEVERITY					
LEVEL	**1**	**2**	**3**	**4**	**5**
5	M	M	H	H	H
4	M	M	M	H	H
3	L	M	M	H	H
2	L	L	M	M	M
1	L	L	M	M	M

6. Level of concern

High:
If operation of the device directly affects the patients and/operator so that failures or latent flaws could result in death or serious injury to the patient and/or operator. Also considered 'high' if the device indirectly affects the patient and/or operator (e.g. through the action of care provider) such that incorrect or delayed information could result in death or serious injury of the patient and/or operator.

Medium:
If the operation of the device directly affects the patient and/or operator so that failures or latent design flaws could result in non-serious injury to the patient and/or operator. Also considered 'medium' if the device indirectly affects the patient and/or operator (e.g. through the action of a care provider) where incorrect or delayed information could result in non-serious injury to the patient and/or operator.

Low:
If failures or latent design flaws would not be expected to result in any injury to the patient and/or operator.

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the document is approved for use.

Management Approval : Owner			
Name:	Ian Cartland	Role:	Project Manager
Signature:		Date:	

Approval by the Quality Manager (QA), indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the document is approved for use.

Quality Assurance Approval			
Name:	Ricky Dolphin	Role:	Nominated Delegate Quality Manager
Signature:		Date:	

Document History

Version	Date released for approval	Developer Initials	Reviewer Initials	Changes from Previous Version
5.0	29 May 2015	IC	RD	Updated for v6.0 of the Risk Analysis. Updated document template.

1. Purpose

The purpose of this document is to review the Risk Management Plan and the associated documents to determine their compliance with the requirements of EN ISO 14971:2012 Medical Devices – Application of Risk Management to Medical Devices.

2. Introduction

The Risk Management Plan is divided into two phases:

i) Description of the intended use of the device and identification of the characteristics that could affect the safety of the device to patients, carers and the environment. Annex C of EN ISO 14971:2012 will be used to identify the device characteristics that could impact on safety.

ii) Identification of known or foreseeable hazards, using as a guide, Annex E of EN ISO 14971:2012. For each hazard identified, its risk potential will be estimated based on the severity and occurrence likelihood identified in the Risk Management Plan and **SOP QRM-02, Risk Management Process** and the actions taken to reduce the risk(s) identified.

On completion of the above analyses the Project Manager will review the actions to ensure that the risk control measures are appropriate for reducing the risk(s) to an acceptable level. If any residual risk has a 'high' level of concern, the Project Manager will ensure that the medical benefits of the device outweigh the residual risks.

3. Review of medical device characteristics that could impact on safety

QRM-01-001 v4.0 addresses the characteristics that could impact on safety identified in EN ISO 14971:2012, Annex C.

4. Review of hazards

All hazards identified in **QRM-02-001** v6.0 have an acceptable level of concern hence no reports are required to demonstrate that medical benefits of the device outweigh the residual risks.

5. Conclusion

This report confirms that the hazards associated with Cantab Mobile have been identified and the risks associated with each hazard estimated and evaluated. The methods for mitigating these risks have been identified. On completion of this Risk Management Process all residual risks have an acceptable level of concern.

This Risk Management Plan will be reviewed as a result of any negative post market feedback.

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SHORT VERSIONS OF THE GERIATRIC DEPRESSION SCALE: A STUDY OF THEIR VALIDITY FOR THE DIAGNOSIS OF A MAJOR DEPRESSIVE EPISODE ACCORDING TO ICD-10 AND DSM-IV

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ABSTRACT

Objective. To determine the validity of short Geriatric Depression Scale (GDS) versions for the detection of a major depressive episode according to ICD-10 criteria for research and DSM-IV.

Design. Cross-sectional evaluation of depressive symptoms in a sample of elderly subjects with short GDS versions. Different GDS cutoff points were used to estimate the sensitivity, specificity, positive predictive value and negative predictive value for the diagnosis of major depressive episode. Internal consistency of the scales was estimated with the Cronbach's alpha coefficient.

Setting. Mental Health Unit for the Elderly of 'Santa Casa' Medical School in São Paulo, Brazil.

Participants. Sixty-four consecutive outpatients aged 60 or over who met criteria for depressive disorder (current or in remission). Subjects with severe sensory impairment, aphasia or Mini-Mental State score lower than 10 were excluded from the study.

Measurements. ICD-10 Checklist of Symptoms, GDS with 15, 10, 4 and 1 items, Montgomery-Åsberg Depression Rating Scale (MADRS), ICD-10 diagnostic criteria for research and DSM-IV diagnostic criteria.

Results. The use of the cutoff point 4/5 for the GDS-15 produced sensitivity and specificity rates of 92.7% and 65.2% respectively, and positive and negative predictive values of 82.6% and 83.3% respectively when ICD-10 diagnostic criteria for major depressive episode were used as the 'gold standard'. Similarly, rates of 97.0%, 54.8%, 69.6% and 94.4% were found when DSM-IV was the comparing diagnostic criteria. Sensitivity, specificity and positive and negative predictive values for the cutoff point 6/7 were 80.5%, 78.3%, 86.8% and 69.2% according to ICD-10, and 84.8%, 67.7%, 73.7% and 80.8% respectively according to DSM-IV. Intermediate values were found for the cutoff point 5/6. The best fit for GDS-10 was the cutoff point 4/5, which produced a sensitivity rate of 80.5%, specificity of 78.3%, positive predictive value of 86.8% and negative predictive value of 60.2% according to ICD-10 diagnosis of a major depressive episode. Similarly, rates of 84.8%, 67.7%, 73.7% and 80.8% were found when DSM-IV criteria for major depression were used. GDS-4 cutoff point of 2/3 was associated with a sensitivity rate of 80.5%, specificity of 78.3%, positive predictive value of 86.8% and negative predictive value of 69.2% when compared to ICD-10. Again, rates of 84.8%, 67.7%, 73.7% and 80.8% respectively were found when the criteria used were based on DSM-IV. GDS-1 had low sensitivity (61.0% and 63.6% for ICD-10 and DSM-IV respectively) and negative predictive value (56.7% and 67.6% for ICD-10 and DSM-IV respectively), suggesting that this question is of limited clinical utility in screening for depression. GDS-15 (rho = 0.82), GDS-10 (rho = 0.82) and GDS-4 (rho = 0.81) scores were highly correlated with subjects' scores on the MADRS. Reliability coefficients were 0.81 for GDS-15, 0.75 for GDS-10 and 0.41 for GDS-4.

Conclusion. GDS-15, GDS-10 and GDS-4 are good screening instruments for major depression as defined by both the ICD-10 and DSM-IV. The shorter four- and one-item versions are of limited clinical value due to low reliability and failure to monitor the severity of the depressive episode. General practitioners may benefit from the systematic use of short GDS versions to increase detection rates of depression among the elderly. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS depression; GDS; short versions; assessment; screening; diagnosis; ICD-10; DSM-IV; validity; reliability

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Depression is a common and disabling disorder in later life. Epidemiological surveys indicate that 1–16% of the elderly are clinically depressed (Copeland *et al*., 1987; Kay *et al*., 1985; Livingston *et al*., 1990; Roberts *et al*., 1997). In addition, these subjects are significant users of medical services (Koenig and Kuchibhatla, 1998) and are at increased risk of suicide (Cattel and Jolley, 1996; Conwell *et al*., 1996; Draper, 1996). These factors make depression one of the most relevant medical problems among the elderly. However, depressive symptoms often go unrecognized by both patients and medical professionals (Koenig *et al*., 1988; Rabins, 1996; Williams-Russo, 1996), causing unnecessary suffering to those who are untreated, burden to the families and increased financial costs to society (Gurland *et al*., 1997; Lebowitz *et al*., 1997).

Many factors contribute to make the detection of depression in older adults particularly difficult. These include the presence of concurrent medical illness, social isolation, insidious onset of symptoms and the occasional absence of obvious depressed mood (Lebowitz *et al*., 1997; Berger *et al*., 1998; Gallo *et al*., 1997). In fact, the presence of clinically significant symptoms that do not fulfil criteria for a depressive disorder is very common in this age group (Koenig and Blazer, 1996) and the identification of such cases very often depends on the use of systematic assessments.

The Geriatric Depression Scale (GDS) (Yesavage *et al*., 1983) is one of the most widely used instruments for the screening of depression in later life (see Stiles and McGarrahan, 1998 for review). Short forms of the GDS with 1, 4, 10, 15 and 20 questions (as opposed to the 30 questions of the original version) are also available (van Marwijk *et al*., 1995). Their use in clinical practice is even more attractive, as they can substantially reduce administration time. Test–retest reliability indexes for the short versions are usually acceptable (van Marwijk *et al*., 1995; Lyness *et al*., 1997; Shah *et al*., 1996), but their validity for diagnosis of depression according to current diagnostic criteria has not yet been established.

The present study was designed to evaluate the validity of the GDS-15, 10, 4 and 1 for the diagnosis of a major depressive episode according to the ICD-10 diagnostic criteria for research (WHO, 1993) and the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (APA, 1994).

METHODS

Subjects were selected from the outpatient clinic for the elderly (UNID) of the Department of Mental Health of 'Santa Casa' Medical School of São Paulo, Brazil. The characteristics of this service have been published elsewhere (Almeida *et al*., 1998). Briefly, UNID provides medical diagnosis and treatment to a socially deprived segment of the elderly population of the central area of the city of São Paulo. The registration of patients in the unit includes both self and medical referral. For the present study, we recruited 64 consecutive referrals of subjects aged 60 or over who fulfilled ICD-10 criteria for the diagnosis of depressive disorder (current or in remission). Subjects with severe hearing or visual impairment, aphasia or a Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975) score lower than 10 were not included. All subjects were informed about the aims of the study and, after giving their consent, were asked to answer a number of questions assessing socio-demographic features such as age, sex, marital status, place of birth, years of schooling, employment status and family income per capita.

Subjects were then asked to answer the questions of the GDS-15, Brazilian version. Questions were read aloud to all subjects, so that illiterate patients could also be evaluated. The scores for the GDS-10, GDS-4 and GDS-1 were estimated according to van Marwijk *et al*. (1995). The details about the construction of the Brazilian version of the GDS have been described elsewhere (Almeida and Almeida, 1999). In summary, all scale items were converted to Portuguese and back to English by independent translators. The English version was then compared to the original and minor adjustments were made to ensure that the Brazilian scale was an accurate translation of the original. The test–retest reliability of the scale was assessed in a sample of 51 subjects. Weighted kappa for the 15- and 10-item GDS was 0.64 and 0.60 respectively, but only 0.37 and 0.06 for the GDS-4 and GDS-1.

The ICD-10 Symptom Checklist for Mental Disorders (Janca *et al*., 1994) was used to investigate the presence or absence of specific symptoms necessary to fulfil criteria for a depressive disorder. Symptoms were rated according to the information obtained from both the patient and a qualified informant (spouse or children for most cases). This checklist of symptoms was then used to reach the diagnosis of major depressive episode or dysthymia according to ICD-10 diagnostic

criteria for research and DSM-IV. Finally, the Montgomery-Åsberg Rating Scale (MADRS) (Montgomery and Åsberg, 1979; Dratcu *et al*., 1987) was used as a supplementary measure of validity.

Data analysis

The data were analysed using the statistical package 'Stata', version 5. Likelihood ratio analysis of contingency tables was used in the investigation of categorical data, the statistical result being distributed as chi-squared (χ^2). Sensitivity and specificity rates, as well as positive and negative predictive values, were estimated from 2 × 2 tables. One-way analysis of variance was used to estimate score differences among patients with mild, moderate and severe depression. This analysis was followed by *post-hoc* multiple comparisons using the Scheffé method. Kappa statistic was determined as a measure of agreement between ICD-10 and DSM-IV for the diagnosis of major depressive episode. Kappa values indicate if the agreement between measures is poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or very good (0.81–1.00). Spearman correlation coefficients were calculated as a measure of association between GDS total scores for the questionnaires with 4, 10 and 15 items, as well as between MADRS and GDS scores. The internal consistency (reliability) of the various short versions of the GDS was measured using Cronbach's alpha coefficient. Ninety-five per cent confidence intervals (CI) were calculated for groups' means, kappa (CI_{κ}), Spearman correlation coefficients (CI_{Sp}) and for alpha values (CI_{alpha}).

RESULTS

Sixty-four subjects were recruited between March and May 1998. Fifty-four were women (84.4%). Subjects' mean age was 67.45 (CI = 65.98–68.92) and their average monthly income was approximately US$ 256.20 (CI = 163.80–348.50). Twenty-five (39.1%) were currently married and eight (12.5%) were unable to read or write. Subjects' mean MMSE score was 25.30 (CI = 24.33–26.26).

Forty-one (64.1%) and thirty-three (51.6%) subjects fulfilled criteria for major depressive episode according to ICD-10 and DSM-IV respectively. Agreement between the two diagnostic systems was 87.5%, with a kappa value of 0.75 (CI_{κ} = 0.59–0.91). Subjects were then further classified for severity of symptoms according to ICD-10 guidelines. Thirteen (20.3%) met criteria for mild, 16 (25.0%) for moderate and 12 (18.7%) for severe depressive episode. Another two patients fulfilled ICD-10 criteria for dysthymia. Seven subjects (10.9%) fulfilled criteria for dysthymia according to DSM-IV.

The mean GDS-15 score for the whole sample was 7.27 (CI = 6.32–8.21), with values ranging from 0 to 15. Scores varied significantly according to the degree of severity of the depressive episode ($F = 27.71$, $df = 3$, $p < 0.001$). Fig. 1 shows mean GDS-15 scores and the respective 95% confidence intervals for subjects with severe ($N = 12$), moderate ($N = 16$), mild ($N = 13$) and no depression ($N = 23$) according to ICD-10. Scheffé analyses for multiple comparisons showed that patients with severe depression scored on average 3.69 (CI = 0.93–6.45, $p = 0.004$), 4.69 (CI = 1.80–7.59, $p < 0.001$) and 7.96 (CI = 5.38–10.53, $p < 0.001$) more points than subjects with moderate, mild and no depression respectively. Table 1 displays mean score differences for patients with no, mild, moderate and severe depression for both the GDS and MADRS.

Table 1. Mean score differences between levels of depression severity according to ICD-10 using the GDS-15, GDS-10, GDS-4 and MADRS

	No depression	Mild	Moderate
GDS-15			
Mild	3.26(0.005)		
Moderate	4.27(<0.001)	1.00(0.766)	
Severe	7.96(<0.001)	4.69 (<0.001)	3.69(0.004)
GDS-10			
Mild	2.31(0.003)		
Moderate	2.87(<0.001)	0.57(0.841)	
Severe	5.17(<0.001)	2.86(<0.001)	2.29(0.008)
GDS-4			
Mild	1.01(0.010)		
Moderate	1.34(<0.001)	0.33(0.770)	
Severe	2.00(<0.001)	0.99(0.036)	0.67(0.224)
MADRS			
Mild	8.40(<0.001)		
Moderate	12.10(<0.001)	3.70(0.245)	
Severe	21.12(<0.001)	12.72(<0.001)	9.02(<0.001)

Note: Numbers in brackets represent p values for alpha = 0.05 (two-tailed values).

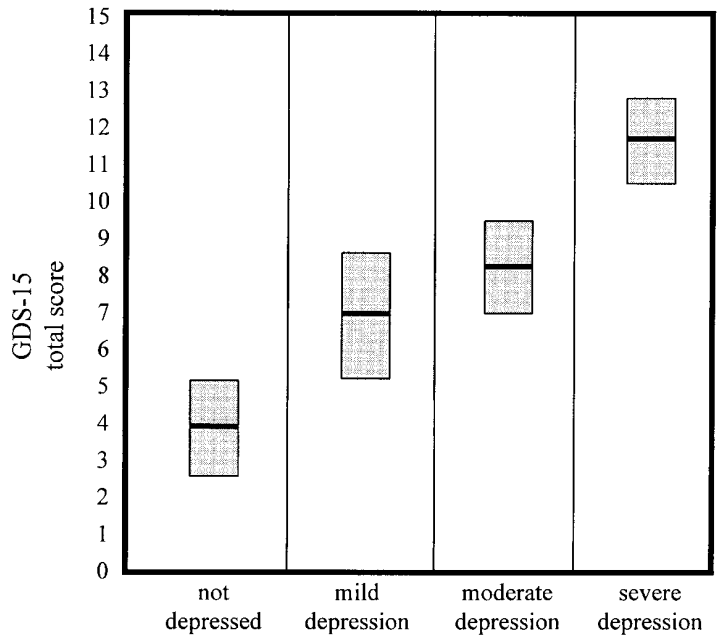

Fig. 1. GDS-15 total scores for subjects with severe, moderate, mild and no depression according to ICD-10 diagnostic criteria for research. Dark lines indicate mean scores. Boxes represent 95% confidence intervals of the mean

Table 2 shows the percentage of patients with depression who answered the 15 GDS questions according to the depressive pattern. Question 2 was the most sensitive GDS-15 item for the detection of depression according to ICD-10 (82.9%) and DSM-IV (84.8%). Table 3 shows sensitivity and specificity rates, as well as positive and negative predictive values, for different GDS cutoff points for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. The use of just one question ('Are you basically satisfied with your life?') to ascertain the presence of depression was

Table 2. Questions included in the GDS-15 and the percentage of patients fulfilling criteria for a major depressive episode according to ICD-10 and DSM-IV who scored within the depression range

	ICD-10 (%)	DSM-IV (%)
Are you basically satisfied with your life?[10,4,1]	61.0	63.6
Have you dropped many of your activities and interests?[10,4]	82.9	84.8
Do you feel that your life is empty?	73.2	75.8
Do you often get bored?	75.6	75.8
Are you in good spirits most of the time?[10]	63.4	60.6
Are you afraid that something bad is going to happen to you?	51.2	60.6
Do you feel happy most of the time?[10,4]	68.3	72.7
Do you feel helpless?[10]	65.8	72.7
Do you prefer to stay at home, rather than going out and doing new things?[10,4]	70.7	72.7
Do you feel you have more problems with your memory than most?	58.5	60.6
Do you think it is wonderful to be alive?	24.4	24.2
Do you feel pretty worthless the way you are now?[10]	48.8	54.5
Do you feel full of energy?[10]	56.1	60.6
Do you feel that your situation is hopeless?	43.9	51.5
Do you think that most people are better off than you are?[10]	63.4	63.6

Note: The numbers 10, 4 and 1 at the side of the questions indicate the items included in the GDS-10, GDS-4 and GDS-1 respectively.

Table 3. Performance of the versions of the GDS at different cutoff points for the detection of a major depressive episode according to ICD-10 and DSM-IV

	ICD-10	DSM-IV
GDS-15 cutoff point 4/5		
Sensitivity	92.7	97.0
Specificity	65.2	54.8
Positive predictive value	82.6	69.6
Negative predictive value	83.3	94.4
GDS-15 cutoff point 5/6		
Sensitivity	85.4	90.9
Specificity	73.9	64.5
Positive predictive value	85.3	73.2
Negative predictive value	73.9	86.9
GDS-15 cutoff point 6/7		
Sensitivity	80.5	84.8
Specificity	78.3	67.7
Positive predictive value	86.8	73.7
Negative predictive value	69.2	80.8
GDS-10 cutoff point 3/4		
Sensitivity	92.7	97.0
Specificity	65.2	54.8
Positive predictive value	82.6	69.6
Negative predictive value	83.3	94.4
GDS-10 cutoff point 4/5		
Sensitivity	80.5	84.8
Specificity	78.3	67.7
Positive predictive value	86.8	73.7
Negative predictive value	69.2	80.8
GDS-4 cutoff point 2/3		
Sensitivity	80.5	84.8
Specificity	78.3	67.7
Positive predictive value	86.8	73.7
Negative predictive value	69.2	80.8
GDS-1		
Sensitivity	61.0	63.6
Specificity	91.3	80.6
Positive predictive value	92.6	77.8
Negative predictive value	56.7	67.6

associated with poor sensitivity and negative predictive values, suggesting that this is not a useful strategy to investigate the presence of depression in clinical practice.

Total scores for the 15-, 10- and 4-item GDS were highly correlated. Spearman correlation coefficients were 0.99 (CI_{Sp} = 0.99–1.00), 0.95 (CI_{Sp} = 0.93–0.97) and 0.96 (CI_{Sp} = 0.93–0.97) for the association between GDS-15 and GDS-10, GDS-15 and GDS-4, and GDS-10 and GDS-4 respectively. Similarly, Spearman coefficients were estimated to explore the association between the total score on the MADRS and GDS-15 (rho = 0.82, CI_{Sp} = 0.72–0.89), GDS-10 (rho = 0.82, CI_{Sp} = 0.72–0.89) and GDS-4 (rho = 0.81, CI_{Sp} = 0.70–0.88). The internal consistency of the short GDS versions was estimated by Cronbach's alpha. Reliability coefficients were 0.81 (CI_{alpha} = 0.73–0.87) for GDS-15, 0.75 (CI_{alpha} = 0.65–0.83) for GDS-10 and 0.41 (CI_{alpha} = 0.13–0.61) for GDS-4.

DISCUSSION

A large number of depression rating scales are currently available for use in clinical and research settings. They all claim to assess the clinical concept of 'depression', although their constructs vary considerably (Snaith, 1993). The choice of a scale should be based on a number of factors, such as its ability to detect cases, assess the severity of symptoms, be sensitive to change over time and indicate when the patient has recovered. Age and cultural factors should not interfere significantly with the performance of the scale. In addition, the scale should be quick to administer and simple to rate.

The Geriatric Depression Rating Scale (GDS) has been widely used in both clinical and research settings (Montorio and Izal, 1996). The scale has been translated to various languages and is available in many Asian (Liu *et al*., 1998), European (Bach *et al*., 1996; Clement *et al*., 1997; Gottfries *et al*., 1997) and Latin American countries (Baker and Espino, 1997). This suggests that the GDS may produce consistent results across different cultures. Short versions of the scale have been introduced with the aim of saving time with its application (Sheikh and Yesavage, 1986).

The GDS with 15 items has been used in various settings, including the community (Dunn and Sacco, 1989; Ingram, 1996), general practice (van Marwijk *et al*., 1995; Lyness *et al*., 1997) and geriatric units (Shah *et al*., 1996, 1997; Herrmann *et al*., 1996). The internal consistency of the GDS-15 has been evaluated by a few studies. Most have reported reliability values around 0.80 (van Marwijk *et al*., 1995; Liu *et al*., 1998; D'Ath *et al*., 1994), which is in line with our findings. These results indicate that the questions included in the GDS-15 assess depression in a coherent and useful way. The GDS-10 has also shown good internal consistency in this study (alpha = 0.75) and others (van Marwijk *et al*., 1995). The use of the shorter

four-item version, however, seems less reliable (alpha = 0.41).

The usefulness of short GDS versions will also depend on their capacity to identify cases of depression in the elderly. For screening purposes one should favour GDS cutoff points that yield high levels of sensitivity and negative predictive values. The use of cutoff points of 4/5 (non-case/case) for the GDS-15, 3/4 for GDS-10 and 2/3 for GDS-4 produced robust results. However, this occurred at the expense of relatively low specificity and positive predictive values, which suggests that the use of higher cutoff points may be more accurate for the diagnosis of a depressive episode. Herrmann *et al*. (1996) suggested that the optimal cutoff score for the GDS-15 was 5/6. This produced sensitivity and specificity rates of 85% and 74% respectively (Herrmann *et al*., 1996). Their results are very similar to those found in the present study, but are in contrast to the cutoff point of 2/3 proposed by van Marwijk *et al*. (1995). In common with Herrmann *et al*. (1996), we recruited patients from a specialized mental health unit for the elderly, whereas van Marwijk *et al*. (1995) selected their sample from a general medical practice. Psychiatric services are more likely to deal with more severe cases of depression and, as a consequence, select samples of patients that produce higher GDS scores—this may move cutoff points upwards. Another important difference between this and the study by van Marwijk *et al*. (1995) is that they used the Diagnostic Interview Schedule (DIS) as their gold standard for the diagnosis of depression. Recent reports suggest that the DIS may produce a substantial number of false positive cases (Regier *et al*., 1998), which would explain the lower GDS cutoff points found by van Marwijk *et al*. (1995).

Severity of symptoms in this study was measured in two different ways: ICD-10 definition of mild, moderate and severe depression, and total score on the MADRS. GDS scores increased with illness severity, as defined by both the ICD-10 and MADRS. However, score differences between mild and moderate cases, according to ICD-10 definition, were not statistically significant. There are two possible explanations for these findings: (1) the ICD-10 definition of mild and moderate depression is not clinically meaningful, and (2) short GDS versions are not sensitive enough to detect differences between mild and moderate cases of depression. The ICD-10 definition of illness severity is based solely on the number of symptoms present during the mental state evaluation. This is clearly an unsatisfactory approach, as it fails to assess the severity of specific symptoms. The same applies to the scores of the GDS. Interestingly, however, GDS scores for all short versions (excluding the GDS-1) were highly correlated with the MADRS, which is a well-accepted measure of severity of symptoms (Maier *et al*., 1988). Therefore, in practical terms, GDS scores are indicative of illness severity even though the scale does not evaluate symptom severity. GDS-15 scores below 5 seem to indicate the absence of clinically significant depressive symptoms. There is, then, a great deal of overlap between scores indicative of mild and moderate depression according to ICD-10. Tentative scores of 5–7 and 8–9 on the GDS-15 may be used for mild and moderate depression respectively. Scores of 10 or more indicate the presence of a severe depressive episode. In addition, if GDS scores can be used as an indication of the severity of illness, one would expect the scale to monitor change over time reliably. Unfortunately, there are not as yet enough data to support this hypothesis. Finally, shorter GDS versions (GDS-10 or lower) may be less helpful in assessing illness severity, as the limits between mild, moderate and severe depression become increasingly less clear with the reduction of GDS items.

In summary, our results show that the 15- and 10-item GDS can reliably detect the presence of a major depressive episode among older adults. Shorter versions are less reliable and informative. The total score on the GDS-15 indicates illness severity, although the scale does not assess the

KEYPOINTS

- Short GDS scales are quick to apply and simple to rate
- The short forms of the GDS with 10 and 15 items are reliable screening instruments for major depression according to ICD-10 and DSM-IV. Their regular use in medical practice is likely to increase the detection of clinically significant depressive symptoms in older adults
- Different cutoff points are likely to be useful for clinical and research purposes
- The total scores on the GDS with 10 and 15 items are reliable measures of the severity of the depressive episode

severity of specific symptoms. Short GDS scales are quick to apply and simple to rate. Their regular use in general medical practice should be encouraged as a means of increasing professional and public awareness of depression among the elderly, and as an effective way of identifying subjects with significant depressive symptoms.

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DEVELOPMENT AND VALIDATION OF A GERIATRIC DEPRESSION SCREENING SCALE: A PRELIMINARY REPORT

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Summary—A new Geriatric Depression Scale (GDS) designed specifically for rating depression in the elderly was tested for reliability and validity and compared with the Hamilton Rating Scale for Depression (HRS-D) and the Zung Self-Rating Depression Scale (SDS). In constructing the GDS a 100-item questionnaire was administered to normal and severely depressed subjects. The 30 questions most highly correlated with the total scores were then selected and readministered to new groups of elderly subjects. These subjects were classified as normal, mildly depressed or severely depressed on the basis of Research Diagnostic Criteria (RDC) for depression. The GDS, HRS-D and SDS were all found to be internally consistent measures, and each of the scales was correlated with the subject's number of RDC symptoms. However, the GDS and the HRS-D were significantly better correlated with RDC symptoms than was the SDS. The authors suggest that the GDS represents a reliable and valid self-rating depression screening scale for elderly populations.

INTRODUCTION

MOST EXISTING depression rating scales have been developed and validated in younger populations and their applicability with older persons has not yet been demonstrated. The scale described in this article was specifically designed to measure depression in the aged, primarily as a screening instrument, and validated within this population.

MEASURING DEPRESSION IN THE AGED

The need for a geriatric depression scale is obvious. Between 5 and 20% of the 20 million aged Americans are estimated to be depressed (GURLAND, 1976). Although one could apply existing general psychiatric depression scales to this population, the aged present unique problems for clinicians and researchers interested in the study and treatment of depression (SALZMAN and SHADER, 1978).

A major problem is the confusion of dementia with depression in the elderly. The syndrome of "pseudodementia", with psychomotor retardation and passive refusal to

respond appropriately to cognitive tests is depression mistaken for dementia (WELLS, 1979; JARVIK, 1976). Depression in the elderly often is accompanied by subjective experiences of memory loss and cognitive impairment (KAHN *et al.*, 1975), symptoms seen less frequently in the young.

Conversely, somatic symptoms which are usually a key to diagnosis of depression in the young are less useful in the elderly. For instance, sleep disturbances are a common symptom of endogenous depression; but such disturbances are also common in the nondepressed elderly (COLEMAN *et al.*, 1981), while rare in younger persons not suffering from depression. A host of other examples include the normal decline of sexual function, constipation, and the aches and pains associated with arthritis in the aged.

The high prevalence of somatic complaints among the elderly and their unique cognitive complaints present both a problem and an opportunity in screening for depression in the elderly. The problem is that most existing scales are heavily loaded toward measuring the somatic symptoms of depression. Although somatic complaints are clearly part of major depressive disorders, this will not necessarily be the case in milder forms of depression. Moreover, to the extent one is interested in screening for depression rather than formal diagnosis or description, discrimination between depressed and nondepressed persons or between different degrees of depression would seem to be the primary concern. For this reason it may be necessary to weight somatic symptoms of depression less heavily than psychological symptoms having greater discriminative power. On the other hand, the unique cognitive complaints of the elderly may present an opportunity to devise screening instruments with enhanced discriminative power in the elderly.

Another problem in the assessment of geriatric depression and other disorders experienced by the aged is that the elderly are typically more resistant to psychiatric evaluation than younger patients (SALZMAN and SHADER, 1978; WELLS, 1979). Consequently, one needs to design the items comprising a scale to fit this population; questions appropriate for use with the young may not be appropriate for the old. For example, questions about sexuality often make the elderly defensive, and yet they are included on many existing scales. Other questions may pose problems of patient acceptance as well as leading to problems of interpretation (BLUMENTHAL, 1975). For example, questions about suicidal intent, whether life is worth living, or whether one is hopeful about the future obviously have different meaning in those reaching the end of their lifespan. Of course these problems of patient resistance and unique interpretation can probably be dealt with adequately if an experienced interviewer administers the depression scale, and the scale is designed to elicit more open-ended responses from the patient in an atmosphere fostering good rapport. However, in designing a self-rating depression scale for the aged, these issues need to be adequately addressed in the scale's initial development.

It is also essential to provide a simple, easily understood format in the development of a geriatric depression scale. Several of the self-rating scales presently available may be too difficult for the elderly to complete by themselves. For example, Zung's (1965) self-rating scale for depression uses a four-point scale that is likely to be more confusing than a yes/no format, because it involves a greater number of choices and subtle discriminations that must be made by the person.

The scale reported here was designed to avoid most of these problems associated with

the measurement of geriatric depression by developing the scale with the aged in mind and by selecting items for the scale based on their performance within this population. Questions that proved to have inadequate power to discriminate depressed from non-depressed elderly were not incorporated into the scale while uniquely discriminating items that might not be as useful with younger groups were included. Furthermore, a yes/no format was used in order to make the scale a simple one that could be used in nearly all instances as a self-rating scale and one that would be acceptable to patient and physician alike.

EXISTING DEPRESSION SCALES

There are numerous depression rating scales currently available. These have been subject to several reviews (CARROLL *et al.*, 1973; KOCHANSKY, 1979; MCNAIR, 1979; HEDLUND and VIEWEG, 1979) and include: Hamilton Rating Scale for Depression (HRS-D), Zung Self-Rating Depression Scale (SDS), Beck Depression Inventory, Phenomena of Depression Scale, Grading Scale for Depressive Reactions, Psychiatric Judgment of Depression Scale, NIMH Collaborative Depression GDS, SAD-GLAD, Verdum Depression Rating Scale, CES-D, SCL-90 Profile of Mood States, and the MMPI Depression Scale.

These scales represent a mixture of observer-rated and self-rating scales. In some cases the same scale may also have been designed to function in either manner or an observer-rated measure of depression has been adapted for use as a self-rating scale. CARROLL *et al.*'s (1973) adaptation of the HRS-D represents an example of the latter approach. A problem with adapting a scale from one format to the other, however, is that questions which may have been acceptable to respondents in an interview setting where good rapport is established by the interviewer may no longer be accepted by the respondent when the same questions are asked using a self-rating scale. We have found this to be the case, for example, with Carroll *et al.*'s scale; mildly depressed subjects dislike the disease-oriented questions and have difficulty with questions which assume they are in a hospital setting.

However, the primary problem with these depression scales is that they were not originally designed for use with the elderly and rarely have they been properly validated in this population. There are some exceptions. There has been an attempt to validate the SDS in the aged, but the ability of the SDS to discriminate nondepressed from depressed elderly was found to be limited (ZUNG and GREEN, 1973). Zung suggested using a classification criterion of 40 for depression; although this would correctly identify 88% of depressives, it leads to the false identification of normal elderly as being depressed in 44% of the cases. Other comprehensive reviews suggest that there are still no better criteria that would reduce the number of false positives associated with the SDS (CARROLL *et al.*, 1973; CARROLL, 1978). Thus, although this represents the best validation efforts in this population to date, the SDS still has limitations as a geriatric depression screening device.

Despite the virtual absence of studies aimed at validating existing depression scales within elderly populations, these scales may prove to be useful even though they were not originally designed with the aged in mind. For this reason two of the existing scales were included in the present research. Their inclusion also was desirable so that comparisons between the GDS with currently existing measures could be made. The present research

was not aimed, however, at demonstrating the superiority of the proposed scale over those currently available. Indeed, the enormous number of existing scales would make this a tremendous undertaking. Rather, existing scales were included in order to provide additional information about the convergent validity of the GDS and to enable tentative norms for the GDS to be compared to those for other, more extensively researched measures.

The first of these was the Hamilton Rating Scale for Depression or HRS-D (HAMILTON, 1960). It was intended to be a measure of treatment outcome rather than as a screening device. Unlike the GDS it is designed to be completed by an experienced observer after a 30 min clinical interview which assays most phenomena associated with "endogenous" depression, e.g. insomnia, decreased libido, loss of appetite (LYERLY, 1978). The HRS-D is probably the most widely accepted clinical interview for depression. It has been shown to be a rapidly learned and reliable measure (HAMILTON, 1967) capable of distinguishing between different degrees of depression (CARROLL *et al.*, 1973; BIGGS *et al.*, 1978; KNESEVICH *et al.*, 1977) and to be one of the few scales available that is also useful as a diagnostic instrument (SCHNURR *et al.*, 1976).

The other scale included in the present research was the Zung Self-Rating Scale for Depression or SDS (ZUNG, 1965). It was administered because of its popularity and the availability of norms for elderly subjects. The SDS has been found to be internally consistent with split-half reliability coefficients in the range of 0.73–0.79. However, validity coefficients have shown greater variability across studies; correlations with the HRS-D have ranged from 0.22 to 0.95 (HEDLUND and VIEWEG, 1979). Although quite widely used among clinicians and researchers working psychiatry, the SDS has recently come under criticism as both a research measure and clinical screening device (CARROLL *et al.*, 1973).

Two studies were conducted in the process of developing and validating the Geriatric Depression Scale (GDS). In the first study, a large pool of items were constructed and then tested for the extent to which they appeared to measure depression in the aged. In the second subject, a subset of these items were selected, readministered to a new sample of subjects, and validated against an independent criterion of depression. The latter study also provided a basis for comparing properties of the GDS to other existing measures of depression due to the inclusion of the SDS and HRS-D. These studies will be discussed in turn. Finally, after describing the results of these studies, a number of recent investigations aimed at demonstrating the performance of the GDS in more specific elderly populations will be discussed.

STUDY ONE: ITEM SELECTION

Methods

A team of clinicians and researchers involved in geriatric psychiatry selected 100 questions believed to have potential for distinguishing elderly depressives from normals. In choosing these questions care was taken to include material covering a wide variety of topics relevant to depression, such as somatic complaints, cognitive complaints, motivation, future/past orientation, self-image, losses, agitation, obsessive traits, and mood itself. A yes/no format was chosen for ease of administration since our experience

with the SDS indicated that a range of possibilities often confused elderly patients. Questions also were phrased in a format that would not alarm patients or make them overly defensive. We thought that these features of the scale would maximize its use as a self-rating instrument of depression in the elderly.

After selecting these items for inclusion in the questionnaire, it was administered in its self-rating form to 47 subjects. The subjects were either normal elderly living in the community with no complaints of depression and no history of mental illness, or subjects hospitalized for depression. Both male and female patients were included from a number of hospitals in Santa Clara County California. All subjects were over 55 years old.

Results

Data analysis was based on the rationale that the 100 item scale should have *prima facia* validity for depression and that those items which correlated best with the total score would be most likely to measure depression. The 30 items (Table 1) correlated highest and most significantly with the total score were chosen for inclusion in the GDS. The median correlation among these items was 0.675 (range = 0.47–0.83). For the 100-item, the median correlation was 0.51 (range = −0.07 to 0.83).

TABLE 1. GERIATRIC DEPRESSION SCALE

Choose the best answer for how you felt over the past week

1.	Are you basically satisfied with your life?	yes / no
2.	Have you dropped many of your activities and interests?	yes / no
3.	Do you feel that your life is empty?	yes / no
4.	Do you often get bored?	yes / no
5.	Are you hopeful about the future?	yes / no
6.	Are you bothered by thoughts you can't get out of your head?	yes / no
7.	Are you in good spirits most of the time?	yes / no
8.	Are you afraid that something bad is going to happen to you?	yes / no
9.	Do you feel happy most of the time?	yes / no
10.	Do you often feel helpless?	yes / no
11.	Do you often get restless and fidgety?	yes / no
12.	Do you prefer to stay at home, rather than going out and doing new things?	yes / no
13.	Do you frequently worry about the future?	yes / no
14.	Do you feel you have more problems with memory than most?	yes / no
15.	Do you think it is wonderful to be alive now?	yes / no
16.	Do you often feel downhearted and blue?	yes / no
17.	Do you feel pretty worthless the way you are now?	yes / no
18.	Do you worry a lot about the past?	yes / no
19.	Do you find life very exciting?	yes / no
20.	Is it hard for you to get started on new projects?	yes / no
21.	Do you feel full of energy?	yes / no
22.	Do you feel that your situation is hopeless?	yes / no
23.	Do you think that most people are better off than you are?	yes / no
24.	Do you frequently get upset over little things?	yes / no
25.	Do you frequently feel like crying?	yes / no
26.	Do you have trouble concentrating?	yes / no
27.	Do you enjoy getting up in the morning?	yes / no
28.	Do you prefer to avoid social gatherings?	yes / no
29.	Is it easy for you to make decisions?	yes / no
30.	Is your mind as clear as it used to be?	yes / no

Although twelve of the 100 original items assessed somatic complaints (e.g. sleep disturbance, anorexia, weight loss, cardiac or gastrointestinal symptoms), none of these were among the 30 items which correlated strongest with the total score. The median correlation between the somatic items and the total score was 0.33 (range = 0.02–0.45). Thus, these items were excluded from the final scale, because they did not meet the purely empirical criterion adopted as a basis for an item's inclusion.

Of the 30 questions selected for inclusion in the GDS, 20 indicated the presence of depression when answered positively while ten others (Nos 1, 5, 7, 9, 15, 19, 21, 27, 29 and 30) indicated depression when answered negatively. The questions were arranged in a 30 item, one-page format and ordered so as to maximize patient acceptance of the questionnaire. Having arrived at a final version of the GDS, a validation study was implemented.

STUDY TWO: VALIDATION

Method

Two groups of geriatric subjects were chosen for the validation phase. The first of these ($n = 40$) consisted of normal elderly persons recruited at local senior centers and housing projects. These subjects had no histories of mental illness and were functioning well in the community. The second group ($n = 60$) consisted of subjects under treatment for depression. These subjects were both inpatients and outpatients, male and female, and in Veterans Administration, county and private treatment settings.

The subjects under treatment were further differentiated into mild and severe depression groups. The frequently used criteria of outpatient vs inpatient groups was not used because in some settings, such as the county mental health service, many severe depressives were outpatients while in other settings, such as the Veterans Administration, many mild depressives were inpatients. Instead, it was decided to divide our group of clinically depressed subjects into mild and severe groups on the basis of whether or not they met Research Diagnostic Criteria (RDC) for a major affective disorder (depressed) (SPITZER *et al.*, 1978). These criteria, elicited during a clinical interview, involve eight symptoms: weight loss, sleep difficulty, loss of energy, psychomotor retardation, loss of interest or pleasure in usual activities, feelings of self-reproach or guilt, complaints of diminished ability to concentrate and recurrent thoughts of death or suicide. Five are required to make the diagnosis. Using these criteria it was possible to separate the depressives into a "mild" group ($n = 26$), having an average of 3.4 RDC criteria symptoms, and a "severe" group ($n = 34$) with an average of 5.9 RDC criteria symptoms. These two groups then became our second and third subject groups, respectively.

The subjects in all groups were given a clinical interview lasting 30–60 min which involved a rating of the HRS-D and the administration of the two self-rating scales, the SDS and our GDS. The interviews were conducted by trained observers, the authors. Interrater reliability on the HRS-D was 0.9. For those subjects who were unable to complete the self-rating scales without assistance, the examiner read the questions orally, elicited answers from the subject, and recorded his or her responses. The order in which the scales were administered was randomly determined for each subject.

Results

Internal consistency and reliability

Four measures of internal consistency were computed for each of the three depression scales. These included: (1) the median correlation between the individual items comprising a scale and the corrected-item total score (total score minus score on the particular time involved); (2) the average intercorrelation among the scale's individual items; (3) CHRONBACH's (1951) alpha coefficient; and (4) the split-half reliability coefficient. Each of these measures or indices of interanl consistency provides a basis for judging the extent to which the scale's items all measure the same underlying construct. In addition to computing these various indices of internal consistency, test–retest data are reported for the GDS. These data provide information regarding the reliability, i.e. stability, of GDS scores over time.

The results of the internal consistency analyses are displayed in Table 2. Each of the indices computed for the depression scales are discussed in turn below.

TABLE 2. COMPUTED INDICES OF INTERNAL CONSISTENCY FOR THE GDS, SDS AND HRS-D

Index	Scale GDS	SDS	HRS-D
Median correlation with total score	0.56	0.44	0.56
Mean interitem correlation	0.36	0.25	0.34
Alpha coefficient	0.94	0.87	0.90
Split-half reliability	0.94	0.81	0.82

Correlation with total score. The median correlation between the items of the GDS and the corrected-item total scores was 0.56 (range = 0.32–0.83), suggesting that all of the items on this scale do, in fact, measure a common latent variable. The comparable values for the SDS and HRS-D were 0.44 (range = 0.24–0.71) and 0.56 (range = 0.16–0.81), respectively. Based on these data it would appear that the GDS, HRS-D and SDS are all internally consistent measures.

Inter-item correlations. The mean intercorrelation among items from the GDS was 0.36; the computed values for the SDS and HRS-D were 0.25 and 0.34, respectively. These values are in a range necessary for a high degree of internal consistency for each scale as a whole, as confirmed by the analyses which follow.

Alpha coefficient. CHRONBACH's (1951) alpha coefficient was utilized in order to provide an overall measure of the internal consistency of the GDS. The computed value of the alpha coefficient was 0.94, suggesting a high degree of internal consistency for the GDS. Computed values of the alpha coefficient for the SDS and HRS-D were 0.87 and 0.90, respectively.

Split-half reliability. An alternative index of internal consistency is the split-half reliability coefficient. This measure is typically derived by splitting a scale into two equivalent forms, calculating their intercorrelation, and then estimating the reliability of the composite scale using the Spearman–Brown formula (NUNNALLY, 1967). Employing this procedure, the reliability coefficients for the GDS, SDS, and HRS-D were found to be 0.94, 0.81, and 0.82, respectively. These values are reported in order to allow comparisons with previous research.

Test–retest reliability. Test–retest reliability was calculated for the GDS by having 20 subjects complete the questionnaire twice, one week apart. A correlation of 0.85 was obtained ($p < 0.001$), suggesting that, at least within the time frame considered here, scores on the GDS reflect stable individual differences.

Validity

The primary test of the validity of the GDS as a measure of depression was provided by the classification of subjects as normal (i.e. nondepressed), mildly depressed, or severely depressed on the basis of RDC for major affective disorder. If both this classification variable and the GDS are valid indices of depression, one would expect normal subjects to receive the lowest GDS scores whereas severely depressed subjects should score the highest on this measure. As a test of this hypothesis, an analysis of variance was conducted in which the classification variable served as a between-subjects factor while the subjects' total scores on the GDS served as the dependent measure. Similar analyses were also performed on the SDS and HRS-D. The results of these analyses provided evidence for each of the scales' validity. In each analysis the main effect for the classification variable was highly significant [GDS: F (2, 97) = 99.48, $p < 0.001$; SDS: $F(2, 97) = 44.75$, $p < 0.001$; HRS-D: $F(2.97) = 110.63$, $p < 0.001$], and as seen in Table 3, in each case the means were ordered as predicted. t-Tests conducted between each pair of means within the same row of this table showed that subjects classified as normal scored significantly lower on each of the scales compared to the mildly and severely depressed subjects while the severely depressed group scored higher than each of the other two groups (all $p < 0.001$). These findings, then, provide evidence

TABLE 3. MEANS AND STANDARD DEVIATIONS FOR THE GDS, SDS, AND HRS AS A FUNCTION OF SUBJECT CLASSIFICATION

Scale	Group Normal	Mildly depressed	Severely depressed	Total sample
GDS	5.75 (4.34)	15.05 (6.50)	22.85 (5.07)	13.98 (9.02)
SDS	34.31 (6.66)	44.15 (11.39)	52.79 (7.51)	43.15 (11.53)
HRS	5.43 (4.98)	13.35 (5.98)	25.42 (6.45)	14.29 (10.35)

*Standard deviations appear in parentheses.

for the validity of the GDS as a measure of depression as well as validating the SDS and HRS-D.

Given previous findings indicating that the SDS (ZUNG, 1965; HEDLUND and VIEWEG, 1979) and HRS-D (CARROLL *et al.*, 1973; HAMILTON, 1960, 1967; BIGGS *et al.*, 1978; KNESEVICH *et al.*, 1977) are valid measures of depression, positive correlations between these measures and the GDS would provide evidence for the scales' convergent validity. The obtained correlation between the GDS and the SDS was found to be 0.84 while a correlation of 0.83 was found between the GDS and the HRS-D. The correlation between the SDS and the HRS-D was 0.80. All of these correlations were statistically reliable at or beyond the 0.001 level.

These analyses provided additional evidence of the validity of each of these depression scales. However, given the criticism that the SDS often may not adequately distinguish between different levels of depressive symptomatology (CARROLL *et al.*, 1973) a comparison was also made across the three scales to determine the relative strength with which each one was related to the RDC. The correlation of each of the depression scales with the classification variable derived from these criteria was computed, and then, following FERGUSON (1971), the magnitude of each correlation was compared to the other two. The obtained correlations between the classification variable and the GDS, SDS, and HRS-D were 0.82, 0.69, and 0.83, respectively. All of these represented statistically reliable correlations (all p's < 0.001). However, comparing each of these correlations to the others showed that, whereas those associated with the GDS and the HRS-D did not differ significantly from each other, t (97) < 1, both of these were significantly greater in magnitude than that associated with the SDS [GDS vs SDS: t (97) $= 3.83$, $p < 0.001$; HRS-D vs SDS: t (97) $= 3.85$, $p < 0.01$]. It thus appears that, compared to the other two measures, the SDS discriminates less effectively between the normal, mildly depressed, and severely depressed subjects.

DISCUSSION

These results provide evidence that the GDS is a reliable and valid measure of geriatric depression. A high degree of internal consistency was found for the scale, and total scores on the GDS were reliable over a one-week interval. Evidence for the validity of the scale came from a comparison of the mean scores associated with subjects classified as normal, mildly depressed, or severely depressed based on RDC criteria for depression; the three groups' means were reliably different and ordered as one would expect given their differing RDC scores.

The primary purpose for constructing the GDS was to provide a reliable screening test for depression in elderly populations that would be simple to administer and not require the time or skills of a trained interviewer. The fact that the GDS was found to discriminate between groups of normal, mildly depressed, and severely depressed subjects is encouraging in this regard. However, one would ultimately desire information on the percentage of individuals correctly and incorrectly classified using particular scores on this measure. This can be accomplished by computing indices of *sensitivity* and *specificity* for the measure, where in this case sensitivity refers to the number of depressed persons correctly classified as depressed based on a particular criterion and where specificity refers

to the number of nondepressed persons correctly classified as such. Sensitivity is lowered to the extent depressed persons are missed using a criterion and classified incorrectly as nondepressed whereas specificity declines to the extent nondepressed persons are incorrectly labelled as suffering from depression.

Sensitivity and specificity of the GDS was examined in a recent study conducted by our research group (BRINK *et al.*, 1981). It was found that among elderly persons drawn from the same centers as those used in the present study, a cut-off score of 11 on the GDS yielded a 84% sensitivity rate and a 95% specificity rate. A more stringent cut-off score of 14 yields a slightly lower, 80%, sensitivity rate, but results in the complete absence of nondepressed persons being incorrectly classified as depressed, i.e. a 100% specificity rate. Based on these findings BRINK *et al.* (1981) suggested that a score of 0–10 be viewed as within the normal range while 11 or greater being a possible indicator of depression. Criteria for the SDS and HRS-D were also offered; these were scores of 46 and 11, respectively. A score of 46 on the SDS achieves 80% sensitivity and 85% specificity whereas a score of 11 on the HRS-D achieves 86% sensitivity and 80% specificity. The three scales, however, are best compared by holding either sensitivity or specificity constant. With specificity held constant at 80%, the sensitivities of the GDS, SDS and HRS-D were found to be 90, 82, and 86%, respectively.

A geriatric depression scale should not only be applicable for screening depression in the physically healthy elderly but should also be useful with the physically ill, and cognitively impaired. There is some evidence that the GDS may fulfill this criterion. Using data from a study by GALLAGHER *et al.* (1981), we found that the GDS differentiated depressed from nondepressed elderly in a sample of subjects who all suffered from physical illness. These subjects were elderly arthritics who had been given the GDS after having been classified as either depressed or nondepressed based on a comprehensive clinical interview. Comparing the GDS scores of these two groups of arthritics it was found that the mean score of the depressed subjects (13.1, S.D. = 7.14) was indeed significantly higher than that of the nondepressed subjects (5.10, S.D. = 4.21), $t\,(47) = 4.94$, $p < 0.001$. These data, then, provide evidence that the validity of the GDS is not limited to elderly subjects who are physically healthy.

In another recent study the GDS was found to differentiate depressed from non-depressed elderly undergoing cognitive treatment for senile dementia. These subjects were classified as demented by criteria of FOLSTEIN *et al.*'s (1975) Mini-Mental Status Exam. It was found that those subjects categorized as depressed by a therapist blind to GDS scores received a mean score of 14.72 (S.D. = 6.13) on the GDS vs a mean of only 7.49 (S.D. = 4.26) for nondepressed subjects, $t\,(41) = 4.4$, $p < 0.001$. Although the results of this study should only be viewed as suggestive since the number of subjects was small ($n = 43$), this study provides preliminary evidence that the GDS is a valid measure of depression with demented, as well as normal, elderly subjects.

However, despite evidence for each of the three scales' validity, they did not appear to perform equally well with respect to the task of differentiating between various RDC defined degrees of depression. Because the GDS and HRS-D were correlated with the number of RDC symptoms each subject had to a significantly greater extent than the SDS, one could argue that, among the two self-rating scales, the GDS appears to provide a

more sensitive screening instrument. Although the SDS was found to correlate more poorly with the RDC than either the GDS or HRS-D, differences in the content and format of the three scales should be considered in making this comparison. It is important to recognize, first of all, the similarity between the three scales and the criterion, the RDC. The HRS-D would be expected to be more strongly related to the RDC, and the group classification variable, than the other two scales simply because the RDC are heavily represented on the HRS-D. Thus, the GDS and SDS are at a disadvantage in the analyses undertaken in the present study, because they do not measure all of the symptoms comprising the RDC while measuring others (e.g. diurnal symptom variation) which are not reflected in these criteria. Moreover, the poorer performance of the SDS may have been due partly to the fact that the RDC measure the severity of depression while the SDS measures the frequency of symptoms, and the two may not correspond closely (CARROLL *et al.*, 1973).

The RDC were chosen as the basis for classifying the level of depression in subjects because of a consensus among researchers that it appears to capture the essential aspects of depressive disorders. Given its wide acceptance, and the lack of a better set of criteria, the failure of a scale to correlate well with the RDC probably reflects more upon the scale in question than the RDC. However, despite the differences in content between the RDC and the GDS, the GDS total score was found to still correlate as strongly with the number of RDC symptoms as the HRS-D whose content corresponds more closely with these criteria. Thus, emphasizing the subjective aspects of depression rather than the somatic and behavior aspects does not seem to have detracted from the validity of the GDS as it may have in the case of the SDS. Despite the differences in content betwen the GDS and HRS-D, the former scale did nevertheless appear to be as valid as the HRS-D in the present research. This finding is somewhat surprising given the absence of somatic symptoms on the former and reliance upon them in the latter. This may be explained in part by the fact that both scales assay mood dysphoria and other psychological symptoms of depression, which seem to best discriminate between the depressed and nondepressed aged.

The issue of how well somatic items measure depression in the elderly and discriminate the depressed from nondepressed is one which deserves further attention. In the first study of the present series, the somatic items' median correlation with the total score was only 0.33, compared to 0.68 for the selected questions. A similar pattern emerged for both the SDS and HRS-D in the second study. On the SDS the items most highly correlated with the corrected-item total score were those concerned with the subjective, psychological aspects of depression while the items most poorly correlated with the total score were those dealing with the somatic aspects of depression. The four lowest correlations were those measuring constipation, decreased libido, appetite decrease, and somatic anxiety while the four highest correlations were those measuring personal devaluation, emptiness, depressed mood, and dissatisfaction. Nearly identical findings have been obtained by STEUER *et al.* (1980). They found total scores on the SDS to be most highly correlated with those items measuring dissatisfaction, depressed mood, emptiness and personal devaluation whereas the lowest correlations occurred with those items measuring constipation, somatic anxiety, decreased libido, and agitation. Moreover, they found

further evidence that the somatic items of the SDS may measure depression more poorly than subjective states in elderly patients by computing four sets of factor scores labelled well being, depressed mood, optimism, and somatic symptoms. Not only was the somatic factor correlated the least strongly with the SDS total score, but this factor was the only one found to be significantly correlated with physician health ratings. Thus, this study demonstrates how, even among individuals screened for serious illness, the poorer health of the aged may undermine the power of somatic symptoms to detect depression.

Of course it is possible that the SDS simply does not contain good measures of those somatic symptoms accompanying depressive illness. But this interpretation does not explain the findings in which other measures of depression have been utilized. For example, although less marked than the results found with the SDS, a similar pattern of results was found in the present research when the items from the HRS-D were correlated with the total score: the somatic items generally correlated less strongly than the items measuring loss of interests, depressed mood and anxiety. Similarly, DESSONVILLE *et al.* (1981) using the Schedule for Affective Disorders and Schizophrenia (SADS) have found that, even though the somatic aspects of depression differentiated depressed from nondepressed elderly, the mean differences between the two groups were smaller on the somatic items than those measuring the subjective states of depression.

Clearly more research is needed on the expression of depression within elderly subjects. The fact that the subjects in the present research were all relatively healthy, as were subjects in these additional studies, may have preserved the discriminability of some somatic questions. It remains to be determined whether the somatic items on these scales adequately measure depression in elderly persons who are less healthy. The GDS appears to avoid many of these problems by focusing on the psychological aspects of depression. This is not meant to imply that somatic symptoms should not be measured in cases of depressive illness. Such symptoms need to be assessed when one is concerned with formal diagnosis or when there is the desire to examine changes in the expression of depressive illness. However, when screening is the goal, discrimination between levels of depression is of primary important and somatic questions may be less powerful in this regard than items chosen empirically for their ability to differentiate the nondepressed from the depressed.

Finally, it is important to distinguish instruments to be used for screening, diagnosis and assessment of change. As the above data indicate, all three may find use as screening instruments, even if this was not their original intent. None, however, is a diagnostic tool. Positive results on any of the three scales on screening should be followed up by a clinical interview if significant levels of depressive symptomatology are found and treatment is being considered. On the other hand, the HRS-D has also been shown to be quite sensitive to changes in the level of symptomatology over time (KNESEVICH *et al.*, 1977), and thus, may serve well, as it was originally intended, as a means of gauging changes in the severity of depression. The use of the SDS in outcome research is more controversial (CARROLL *et al.*, 1973; CARROLL, 1978). It remains to be determined if the GDS may be useful for measuring changes in the severity of depression following treatment.

In conclusion, though not a substitute for observer-rated scales or indepth diagnostic interviews, and not yet shown to be treatment sensitive, the GDS appears to be a promising and simple screening instrument which may find other applications through further research.

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Cantab Mobile

12. Substantial Equivalence Discussion

This section is not applicable. This material is covered in the Executive Summary of this submission (Section 10).

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CAMBRIDGE COGNITION

Document History

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Cantab Mobile

14. Sterilization and Shelf Life

Sterilization and shelf-life regulations are not applicable to Cantab Mobile. Therefore, this section is not applicable.

Cantab Mobile

15. Biocompatibility

This section is not applicable.

Cantab Mobile

16. Software

This report outlines Cambridge Cognition's software development lifecycle and procedures relevant to medical device software development with respect to the requirements of *IEC 62304:2006 Medical device software – Software life cycle processes* for class A software systems. Documents referenced in the report are available upon request.

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17. Electromagnetic Compatibility and Electrical Safety

Cantab Mobile's device design does not include an electronic component in which an evaluation of its electromagnetic compatibility (EMC) is applicable. Therefore, this section is not applicable.

Cantab Mobile

18. Performance Testing - Bench

No bench tests were conducted as a part of this 510(k) submission. Therefore, this section is not applicable.

Cantab Mobile

19. Performance Testing - Animal

Animal performance testing is not applicable to Cantab Mobile's testing and development. Therefore, this section is not applicable.

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Appendix D: Cognitive impairment in depression: a systematic review and meta-analysis

The referenced article is shown below

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2013). Cognitive impairment in depression: a systematic review and meta-analysis. Psychological medicine, 1-12.

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REVIEW ARTICLE

Cognitive impairment in depression: a systematic review and meta-analysis

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Background. This review aimed to address the question of whether cognitive impairment should be considered a core feature of depression that may be a valuable target for treatment.

Method. We conducted a systematic review and meta analysis of cognitive function, assessed with a single neuro psychological test battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB), in patients with depression during symptomatic and remitted states. Inclusion of studies comparing patients remitted from depression and controls enabled us to investigate whether cognitive impairment persists beyond episodes of low mood in depression.

Results. Our meta analysis revealed significant moderate cognitive deficits in executive function, memory and attention in patients with depression relative to controls (Cohen's *d* effect sizes ranging from 0.34 to 0.65). Significant moderate deficits in executive function and attention (Cohen's *d* ranging from 0.52 to 0.61) and non significant small/moderate deficits in memory (Cohen's *d* ranging from 0.22 to 0.54) were found to persist in patients whose depressive symp toms had remitted, indicating that cognitive impairment occurs separately from episodes of low mood in depression.

Conclusions. Both low mood and cognitive impairment are associated with poor psychosocial functioning. Therefore, we argue that remediation of cognitive impairment and alleviation of depressive symptoms each play an important role in improving outcome for patients with depression. In conclusion, this systematic review and meta analysis demonstrates that cognitive impairment represents a core feature of depression that cannot be considered an epiphenomenon that is entirely secondary to symptoms of low mood and that may be a valuable target for future interventions.

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Key words: Attention, CANTAB, cognition, depression, executive function, memory.

Introduction

Cognitive impairment is frequently observed in patients suffering from depression and is associated with poor response to treatment (Potter *et al.* 2004; Story *et al.* 2008; Roiser *et al.* 2012). Impaired cognition has been estimated to occur in around two-thirds of depressed patients (Abas *et al.* 1990; Butters *et al.* 2004; Afridi *et al.* 2011). Impaired ability to think, concentrate or make decisions is a DSM-IV-TR (APA, 2000) diagnostic criterion for major depressive episode. Consistent with this, several systematic reviews have demonstrated cognitive deficits in patients suffering from depression (Burt *et al.* 1995; Veiel, 1997; Zakzanis *et al.* 1998; Stefanopoulou *et al.* 2009; Snyder 2013), including first-episode patients (Lee *et al.* 2012).

Impairments in cognition have been found to persist beyond acute episodes of depression, and between one-third and one-half of remitted depressed patients are thought to be affected by cognitive deficits (Abas *et al.* 1990; Bhalla *et al.* 2006; Reppermund *et al.* 2009). Furthermore, one study revealed that 94% of patients who had cognitive impairment while depressed continued to experience deficits in cognition when remitted from depression (Bhalla *et al.* 2006).

To our knowledge, to date, only two groups have reviewed cognitive function in patients remitted from depression (Hasselbalch *et al.* 2011; Bora *et al.* 2013). The review by Hasselbalch *et al.* (2011) included 500 remitted patients (and 472 controls) and revealed impaired cognitive performance in nine of the 11 included studies. Their review also assessed the association between cognitive function and other clinical

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features such as residual depressive symptoms and current medication status. However, drawbacks of this review relate to the large number of different cognitive tests that were used across studies and the lack of implementation of standardized effect sizes to reflect magnitude of impairment. Meanwhile, the review by Bora *et al.* (2013) included 895 remitted patients (and 997 controls) from 27 studies and, using standardized effect sizes, revealed cognitive deficits in a composite measure of global cognition, in individual cognitive domain composites and in a subset of specific tasks. The review also separately assessed cognitive function in early-onset and late-onset patients and included a meta-regression to uncover the influence of other clinical and demographic factors on cognitive performance. Again, a minor drawback of this review is that task-specific analyses were limited to a subgroup of cognitive tests for which there were sufficient data; therefore, cognitive domain and global cognition meta-analyses necessarily included results from a variety of cognitive tests. A review of the longitudinal course of cognitive function in depression revealed that improvements in mood were most closely related to improvements in verbal memory, verbal fluency and psychomotor speed, whereas attention and executive function remained impaired across treatment (Douglas & Porter, 2009).

Our aim was to conduct a systematic review and meta-analysis to investigate the degree of cognitive impairment in patients with depression during symptomatic and remitted states, focusing on studies that used a single neuropsychological test battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB). Our rationale for including only CANTAB studies was to enable assessment of a broad range of cognitive domains but with consistent tasks implemented across reviewed studies, thereby ensuring interstudy homogeneity. We predicted that cognitive deficits would be observable in both depressed and remitted states.

Method

Systematic review

Studies were identified by searching PubMed and Google Scholar using the following search terms: 'Cambridge neuropsychological test automated battery' or 'CANTAB' and any CANTAB test name (e.g. 'Spatial Span') or its acronym ('SSP') and 'depression' or 'depressed' during the period from 1980 to December 2012. The CANTAB neuropsychological tests included in the search involved the domains of executive function, memory, attention and reaction time, as follows.

Executive function

(One Touch) Stockings of Cambridge (OTS/SOC; Owen et al. 1990). This task was derived from the Tower of London test and assesses visual planning, reasoning and impulsivity. Outcome measures analysed were the number/percentage correct or number of moves above the minimum [for all problems or difficult (four/five-move) problems].

Spatial Working Memory (SWM; Owen et al. 1995). This self-ordered search task is based on foraging behaviour and assesses working memory and strategy use. Participants search for tokens without returning to previous token locations. Outcome measure analysed was between-search errors.

Intra Extra Dimensional Set Shift (IED; Rogers et al. 1999). This test of cognitive flexibility, analogous to the Wisconsin Card Sorting Test (WCST), has multiple stages segregating cognitive processes that assess rule learning, rule reversal and attentional set-shifting. Outcome measures analysed were total errors, extra-dimensional shift errors (adjusted) or stages completed.

Spatial Span (SSP; Kempton et al. 1999). This is a task of spatial short-term memory based on the Corsi block-tapping task. Outcome measure analysed was spatial span.

Memory

Delayed Matching to Sample (DMS; Robbins et al. 1994). In this test participants remember the visual features of a complex, abstract target stimulus and select it from a choice of four target patterns after a variable delay. Outcome measures analysed were total/percentage correct (for all trials or 12-s delay trials).

Paired Associates Learning (PAL; Sahakian et al. 1988). In this test participants learn the locations of a progressively increasing number of abstract stimuli. Outcome measures analysed were total errors (adjusted) or first trials correct.

Pattern Recognition Memory (PRM; Owen et al. 1995). This is a two-forced-choice test of abstract visual pattern recognition memory. Outcome measures analysed were total/percentage correct.

Spatial Recognition Memory (SRM; Owen et al. 1995). This two-forced-choice discrimination paradigm tests spatial recognition memory. Outcome measures analysed were total/percentage correct.

Attention

Rapid Visual Information Processing (RVP; Sahakian et al. 1989). This is a continuous performance test that assesses sustained attention, signal detection and impulsivity. Participants monitor a stream of single digits for three-digit target sequences. Outcome measures analysed were target sensitivity or total hits/omissions.

Reaction time

Reaction Time (RTI; Sahakian et al. 1993). This is a test of simple and five-choice reaction time. Outcome measure analysed was five-choice reaction time.

Inclusion criteria

The inclusion criteria for studies were: (1) used DSM or ICD criteria to diagnose major depressive disorder; (2) included a healthy control group; (3) used CANTAB to assess cognitive function in currently depressed patients and/or remitted depressed patients; and (4) reported sufficient data to estimate Cohen's *d* effect sizes, that is the group mean and either standard deviation or standard error data (and number of subjects in each group) were available for both patients and controls.

Our search revealed 24 studies including 784 currently depressed patients (and 727 controls) and six studies including 168 remitted depressed patients (and 178 controls) that met our inclusion criteria (see Table 1). The criteria for remitted depression varied across studies and are shown in Table 1.

Meta-analysis

Meta-analysis was performed using Review Manager (RevMan, 2011). For each study, Cohen's *d* effect sizes (Cohen, 1988) were calculated as the mean difference between test performance scores for patients compared to controls divided by the pooled standard deviation; negative effect sizes reflected deficits compared to controls. Subsequently, for each test, effect sizes were weighted using the inverse variance method within a random-effects model and pooled across all studies with available data. Pooled effect sizes were reported for tests only when data from three or more studies were available. In addition to meta-analyses for currently depressed patients *versus* controls and remitted depressed patients *versus* controls, a separate subanalysis was conducted for currently depressed patients who were unmedicated at the time of assessment *versus* controls. There were insufficient studies of unmedicated remitted depressed patients to include a subanalysis of this population. Influenced by Cohen's convention regarding the magnitude of effect sizes (Cohen, 1988), a Cohen's *d* effect size in the range 0.2 0.35 was considered small, in the range 0.35 0.65 moderate and >0.65 large. Statistical inferences were made based upon analysis of 95% confidence intervals (CIs).

Results

Profile of cognitive deficits in currently depressed patients

Cohen's *d* effect sizes were calculated based on data from 24 studies that used CANTAB tests in 784 currently depressed patients and 727 controls. Fig. 1 shows the weighted, pooled Cohen's *d* effect sizes for the comparison between depressed patients and healthy controls (black bars), and Table 2 presents detailed meta-analysis results.

Currently depressed patients showed significant moderate deficits compared to healthy controls across the cognitive domains of executive function (Cohen's *d* ranged from 0.34 to 0.54), memory (Cohen's *d* ranged from 0.41 to 0.50) and attention (Cohen's *d* was 0.65), and there was no significant deficit in reaction time (Cohen's *d* was 0.07). The non-significant finding for reaction time should be treated with caution because the results seem to have been affected by one study for which depressed patients showed significantly superior performance to controls. Indeed, when this study was excluded, currently depressed patients showed a nearly significant small deficit in reaction time compared to controls (*d*= 0.32, 95% CIs 0.59 to 0.05). Supplementary Fig. S1 (available online) presents forest plots depicting performance of currently depressed patients relative to controls.

Subanalysis: profile of cognitive deficits in unmedicated currently depressed patients

Cohen's *d* effect sizes were calculated based on data from eight studies that used CANTAB tests in 271 currently depressed patients who were unmedicated at the time of assessment and 267 controls. There were sufficient data to calculate weighted, pooled effect sizes for all executive function tasks, all memory tasks, and for the task of attention; insufficient data were available to calculate a weighted, pooled effect size for the reaction time task. Table 2 presents detailed meta-analysis results.

Unmedicated currently depressed patients showed significant moderate deficits compared to healthy controls on one executive function task (SWM; Cohen's *d* was 0.46), two memory tasks (DMS and PRM; Cohen's *d* ranged from 0.33 to 0.36) and the attention task (RVP; Cohen's *d* was 0.59). Although negative Cohen's *d* effect sizes (ranging from 0.06 to 0.49) were recorded for all remaining tasks, the

Table 1. *Study characteristics and patient demographics for currently depressed and remitted depressed comparisons*

First author	Year	Currently depressed patients					Controls		Notes
		n (female)	Age (years)	Diagnostic criteria	Depression symptoms	Medication status	*n* (female)	Age (years)	
Beats	1996	24 (12)	72.0±5.9	DSM III R	HAMD x 29.6±5.1; MADRS 40.3±7.2	Twenty one medicated, three medication free	15 (9)	69.3±6.6	Minimum age of 60
Boeker	2012	28 (13)	39.7±11.4	DSM x; HAMD 21 ⩾24; BDI ⩾24	HAMD 21 28.5±7.0; BDI 25.9±8.2	Nineteen medicated, nine medication free	28 (13)	35.0±7.4	
Braw	2011	25 (14)	54.0±0.9	DSM IV; HAMD 17>14	HAMD 17 31.3±1.3; BDI 30.8±1.4	All unmedicated for 1 month prior to testing	25 (17)	54.2±0.9	Late adulthood group aged 46 65
		30 (16)	35.0±1.0	DSM IV; HAMD 17>14	HAMD 17 32.5±1.1; BDI 33.5±1.4	All unmedicated for 1 month prior to testing	30 (16)	34.5±1.1	Middle adulthood group aged 25 45
		30 (20)	17.1±0.5	DSM IV; CDRS ⩾40	CDRS R 67.5±2.0; BDI 32.6±1.3	All unmedicated for 1 month prior to testing	30 (18)	17.5±0.6	Young adult group aged <25
Cannon	2009	18 (11)	31±11	DSM IV	MADRS 22±5.3; IDS C 27±6.5	All unmedicated (of whom 11 treatment naïve)	19 (11)	31±8.5	Aged 18 55
Elliott	1996	28 (19)	49.9±1.7	DSM III R	HAMD x 22.4±0.8; MADRS 34.0±1.1	All medicated	22 (15)	48.1±1.2	Aged 40 70
Elliott	1997	6 (1)	34.7 (21 48)	DSM IV	HAMD x 23.8 (20 29); MADRS 35.3 (x 39)	Five medicated, one unmedicated	6 (1)	31.0 (18 55)	
Erickson	2005	20 (10)	37.2±11.9	DSM IV	MADRS 25.4±7.1	All unmedicated for 3 weeks prior to testing (of whom four medication naïve)	Matched (not stated)	Matched (not stated)	All had illness onset before age 40
Grant	2001	48	39.0±10.4	DSM IV	HAMD 17 16.7±5.4	All unmedicated patients for 28 days prior to testing	31	40.2±9.7	Demographics are for a larger sample from which these subjects were drawn
Heinzel	2010	20 (11)	40.0±9.9	DSM IV; HAMD 21 ⩾24	HAMD 21 33.1±7.1; BDI 29.9±4.9	All unmedicated for 1 week prior to testing	29 (21)	35.3±7.3	
Kyte	2005	30 (18)	15.3±2.5	K SADS PL	HAMD x 10.9±6.8	Medicated and unmedicated adolescents	49 (29)	15.2±2.1	
Lyche	2010	37 (23)	44.2±12.3	DSM IV	BDI 21.4±11.1	Thirteen medicated, 24 unmedicated	91 (63)	35.8±12.0	
Maalouf	2010	20 (16)	34.2±9.4	DSM IV; HAMD 25 ⩾17	HAMD 5 24.8±5.8	All medicated	28 (19)	31.9±9.4	
Maalouf	2011	20 (17)	15.3±1.6	DSM IV; K SADS PL	CDRS 58.6±10.9	Thirteen medicated, seven unmedicated	17 (9)	15.2±1.8	
Matthews	2008	14 (14)	14.5±1.2	ICD 10; CAPA C	MFQ 41.3±10.4	All medication naïve	14 (14)	14.4±1.0	
Michopoulos	2008	40 (40)	52.7±10.8	DSM IV TR	HAMD 17 20.0±4.0	All medicated	20 (20)	49.8±12.7	

Michopoulos	2006	11 (11)	50.9±10.5	DSM IV	HAMD x 20.8±3.1	All medicated	11 (11)	52.8±14.1	Melancholic subgroup
		11 (11)	47.8±12.3	DSM IV	HAMD x 18.7±4.2	All medicated			Non melancholic subgroup
Murphy	2003	27 (14)	38.9±9.7	DSM IV	HAMD x 23.6±4.2; MADRS 34.3±5.4	Twenty six medicated, one unmedicated	23 (12)	39.1±10.8	
O'Brien	2004	61 (48)	73.9±6.7	DSM IV; MADRS ⩾20	MADRS 30.7±7.1	Mostly medicated (numbers not stated)	40 (30)	73.3±6.7	Aged over 60
Porter	2003	44 (29)	32.9±10.6	DSM IV	HAMD 17 21.1±4.4; MADRS 28.9±5.5; BDI 27.9±10.2	All unmedicated (of whom 26 medication naïve) for 6 weeks prior to testing	44 (29)	32.3±11.4	
Purcell	1997	20 (12)	37.5 (18 52)	DSM IV	HAMD 24 22.6±5.6	Twelve medicated, eight unmedicated for 2 months prior to testing	20 (12)	37.2 (21 60)	
Reppermund	2009	53 (28)	43.5±8.0	DSM IV	HAMD x 25.1±5.1	Fifty medicated, three unmedicated	13 (7)	46.4±9.5	
Swainson	2001	37	60.8±8.6	DSM IV	HAMD x 21.4±6.2	Not stated	39	64.4±8.5	
Sweeney	2000	58 (39)	32.3±9.1	DSM IV	HAMD 17 21.6±4.3	Medicated patients	51 (39)	36.3±9.7	
Taylor Tavares	2007	22 (17)	38.6±8.1	DSM IV	MADRS 25.5±7.5	Unmedicated patients	25 (18)	34.8±8.8	
Tsaltas	2010	15 (15)	47.8±11.7	DSM IV TR	HAMD 24 27.6±5.6	All medicated	15 (15)	49.3±11.6	Non referred subgroup
		15 (15)	48.5±11.2	DSM IV TR	HAMD 24 31.9±6.5	All medicated			Referred subgroup

		Remitted patients						Controls		
First author	Year	*n* (female)	Age (years)	Diagnostic criteria	Euthymia definition	Depression symptoms	Medication status	*n* (female)	Age (years)	Notes
Beats	1996	19 (10)	73.6±5.4	DSM III R	MADRS <10	HAM D 4.7±2.6; MADRS 6.5±4.5	Mostly medicated	15 (9)	69.3±6.6	
Clark	2005*a*	15 (11)	45.2±10.9	DSM IV	HAMD x <9	HAMD x 2.1±2.9	Six medicated, nine unmedicated	46 (23)	39.2±12.2	
Clark	2005*b*									
Herrera Guzman	2010	60	20 50	DSM IV	HAMD 17 <6	HAMD 17 0.7±0.2	All unmedicated	37	20 50	
Maalouf	2011	20 (15)	15.4±1.3	DSM IV; K SADS PL	CDRS ⩽28	CDRS 23.7 ±10.9	Thirteen medicated, seven unmedicated	17 (9)	15.2±1.8	

Table 1 (*cont.*)

First author	Remitted patients						Controls		
	Year	*n* (female)	Age (years)	Diagnostic criteria	Euthymia definition	Depression symptoms	Medication status	*n* (female)	Age (years)	Notes
O'Brien	2004	26	Not stated	DSM-IV	MADRS <8	Not stated	Not stated	40	78 3±6 7	Aged over 60
Weiland-Fiedler	2004	28 (18)	37 8±12 2	DSM-IV	MADRS <6	MADRS 2 1±2 3	All unmedicated for 3 months prior to testing	23 (11)	35 7±10 4	

DSM-x, *Diagnostic and Statistical Manual of Mental Disorders* (APA, 2000); HAMD-17/-21/-24/-25/-x, Hamilton Depression Rating Scale (17-/21-/24-/25-item/unstated version) (Hamilton, 1960); MADRS, Montgomery–Asberg Depression Rating Scale (Montgomery & Asberg, 1979); BDI, Beck Depression Inventory (Beck, 1961); K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (Kaufman *et al.* 1997); CDRS, Children's Depression Rating Scale (Poznanski *et al.* 1979); CAPA-C, Child and Adolescent Psychiatric Assessment – Child Version (Angold & Costello, 1995); MFQ, Mood and Feelings Questionnaire (Angold *et al.* 2002)

Values given as mean±standard deviation or mean (range)

95% CIs crossed zero in all cases. Supplementary Fig. S2 presents forest plots depicting performance of unmedicated currently depressed patients relative to controls.

Profile of cognitive deficits in remitted depressed patients

Cohen's *d* effect sizes were based on data from six studies that used CANTAB tests in 168 remitted depressed patients and 178 controls. There were sufficient data to calculate weighted, pooled effect sizes for three (out of four) tasks in the domain of executive function, two (out of four) tasks in the domain of memory, and for the task of attention; insufficient data were available to calculate a weighted, pooled effect size for the reaction time task. Fig. 1 shows the weighted, pooled Cohen's *d* effect sizes for the comparison between depressed patients and healthy controls (grey bars), and Table 2 presents detailed meta-analysis results.

Patients remitted from depression showed significant moderate deficits compared to healthy controls across the cognitive domains of executive function (Cohen's *d* ranged from 0.53 to 0.61) and attention (Cohen's *d* was 0.52). There was a tendency towards moderate deficits in the domain of memory (Cohen's *d* ranged from 0.22 to 0.54). Although the 95% CIs crossed zero in both cases, they only just crossed zero for PRM (95% CIs were from 1.08 to 0.01). Supplementary Fig. S3 presents forest plots depicting performance of currently depressed patients relative to controls.

Discussion

Our systematic review and meta-analysis revealed that impairments in cognitive function, assessed with a single neuropsychological test battery (CANTAB), were exhibited by currently depressed patients and by patients remitted from depression. Current depression was associated with significant moderate deficits across all tasks within the domains of executive function, memory and attention, with the exception of the SSP task of executive function, for which there was a tendency towards a moderate deficit. Although the systematic review and meta-analysis revealed no reaction time deficit in currently depressed patients, exploratory reanalysis excluding one anomalous study (in which depressed patients showed significantly superior performance relative to controls) revealed a tendency towards a small deficit in reaction time. Analysis of only unmedicated currently depressed patients showed a significant moderate deficit in the domain of attention and significant small and moderate deficits in some, but not all, tasks within the

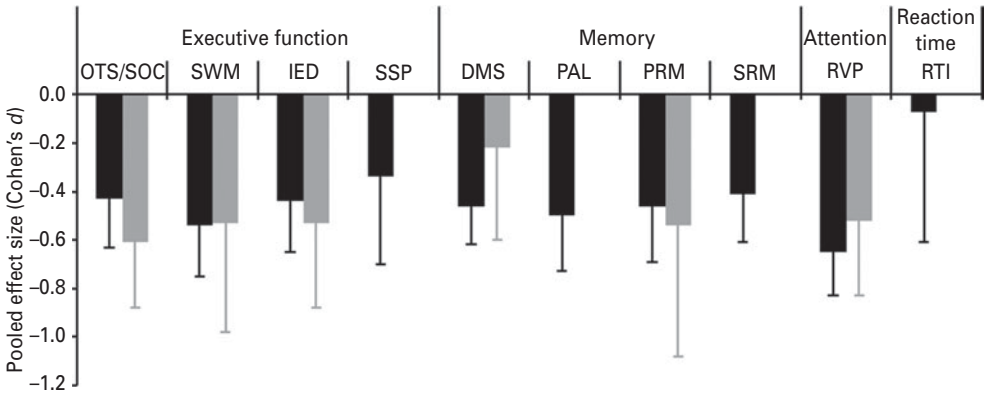

Fig. 1. Pooled, weighted Cohen's *d* effect sizes reflecting the performance of currently depressed patients (black bars) and remitted depressed patients (grey bars) compared to healthy controls on tasks of executive function [OTS/SOC, (One Touch) Stockings of Cambridge; SWM, Spatial Working Memory; IED, Intra Extra Dimensional Set Shift; SSP, Spatial Span], memory (DMS, Delayed Matching to Sample; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; SRM, Spatial Recognition Memory), attention (RVP, Rapid Visual Information Processing) and reaction time (RTI, Reaction Time). Error bars represent 95% confidence intervals (CIs).

domains of executive function and memory. Meanwhile, remitted depressed patients showed significant moderate deficits within the domains of executive function and attention. However, in the domain of memory, remitted depressed patients showed only a tendency towards small/moderate deficits. In summary, our systematic review and meta-analysis demonstrated that cognitive impairment, particularly affecting the domains of executive function and attention, is a core feature of depression that persists during remission in the absence of clinically relevant symptoms of low mood.

The present systematic review and meta-analysis included only studies that had used CANTAB tasks to assess cognitive function in symptomatic or remitted depressed patients relative to controls. To our knowledge, this is the first systematic review and meta-analysis that has focused on studies using a single neuropsychological test battery. The magnitudes of cognitive deficits recorded in the current investigation are broadly in line with those that have been recorded previously. However, our finding of a non-significant deficit in reaction time in currently depressed patients relative to controls contrasted notably with the literature. Nevertheless, following exclusion of one anomalous result, a tendency towards a small deficit on the RTI task was recorded, and the size of this deficit (Cohen's $d=0.32$) was similar to the deficit recorded on the psychomotor speed composite (Cohen's $d=0.33$) in the Snyder (2012) meta-analysis.

Impaired cognitive functioning has been linked with poor response to antidepressant treatment (Potter *et al.* 2004; Story *et al.* 2008). However, the potential clinical relevance of cognitive deficits in depression also depends upon their impact on psychosocial functioning. Impaired psychosocial functioning is a core feature of depression (Weissman *et al.* 2010). It persists in up to 60% of individuals with depression even after mood symptoms of depression have remitted (Jaeger *et al.* 2006), indicating that severity of depressive symptoms cannot fully account for impaired functional ability. For example, patients with subsyndromal depressive symptoms have been found to manifest similar levels of psychosocial dysfunction to those of patients with clinically relevant symptoms (Judd *et al.* 1996). One possible explanation is that persisting cognitive impairments may contribute to poor quality of life and psychosocial functioning in patients whose depressive symptoms have remitted. In support of this, psychosocial functioning has been shown to be associated with performance on measures of attention, executive function, paired associates learning and visuospatial ability in depression (Jaeger *et al.* 2006). Importantly, the association between cognitive deficits and poor psychosocial functioning has been shown to remain significant even when taking into account residual, subclinical depressive symptoms (Jaeger *et al.* 2006).

Another study revealed that severity of cognitive impairment and severity of low mood associate independently with different measures of psychosocial functioning (McCall & Dunn, 2003). Furthermore, in bipolar disorder, psychosocial functioning has been shown to be predicted by both cognition and residual depressive symptoms (Mur *et al.* 2009; Solé *et al.* 2012).

Overall, these findings suggest that remediation of cognitive impairment and alleviation of depressive symptoms may both be involved in improving psychosocial functioning in depression. We therefore argue that cognitive impairment in depression is clinically relevant and may be a valuable target for intervention.

Table 2. *Meta analysis results*

Task	No. patients	No. controls	No. studies	*d*	95% CI	*Z*	*p*	*Q*	I^2 (%)
Currently depressed patients									
OTS/SOC	557	484	16	0.43	0.63 to 0.24	4.32	<0.0001	43.33	56
SWM	567	521	15	0.54	0.75 to 0.33	4.98	<0.00001	43.92	64
IED	578	566	16	0.44	0.65 to 0.23	4.07	<0.0001	52.97	64
SSP	273	217	8	0.34	0.70 to0.01	1.92	0.06	24.19	71
DMS	423	342	12	0.46	0.62 to 0.29	5.37	<0.00001	13.52	19
PAL	321	279	9	0.50	0.73 to 0.26	4.17	<0.0001	18.43	46
PRM	402	347	12	0.46	0.69 to 0.23	3.89	0.0001	25.55	57
SRM	445	371	13	0.41	0.61 to 0.22	4.19	<0.0001	24.38	43
RVP	228	236	7	0.65	0.83 to 0.46	6.75	<0.00001	3.90	0
RTI	157	135	4	0.07	0.61 to 0.46	0.27	0.79	14.33	79
Unmedicated currently depressed patients									
OTS/SOC	191	174	4	0.28	0.68 to 0.11	1.40	0.16	17.21	71
SWM	231	218	6	0.46	0.84 to 0.09	2.43	0.02	25.85	73
IED	171	166	4	0.09	0.46 to 0.28	0.49	0.62	14.00	64
SSP	82	69	3	0.06	0.66 to 0.54	0.20	0.84	6.18	68
DMS	126	112	4	0.36	0.62 to 0.10	2.71	0.007	2.67	0
PAL	106	89	3	0.49	1.22 to 0.23	1.33	0.18	11.02	82
PRM	146	132	5	0.33	0.61 to 0.04	2.23	0.03	5.42	26
SRM	125	112	4	0.29	0.75 to 0.17	1.22	0.22	8.62	65
RVP	123	124	3	0.59	0.84 to 0.33	4.50	<0.00001	1.38	0
Remitted depressed patients									
OTS/SOC	125	109	4	0.61	0.88 to 0.34	4.47	<0.00001	2.80	0
SWM	114	100	3	0.53	0.98 to 0.07	2.28	0.02	5.00	60
IED	62	84	3	0.53	0.88 to 0.18	2.95	0.003	1.51	0
DMS	74	80	3	0.22	0.60 to 0.15	1.16	0.24	2.69	26
PRM	73	78	3	0.54	1.08 to 0.01	1.92	0.05	5.24	62
RVP	123	123	4	0.52	0.83 to 0.21	3.31	0.0009	3.87	22

d, Weighted, pooled Cohen's *d* effect size; CI, confidence interval; *Q*, heterogeneity; I^2, percentage of total variability due to heterogeneity; OTS/SOC, (One Touch) Stockings of Cambridge; SWM, Spatial Working Memory; IED, Intra Extra Dimensional Set Shift; SSP, Spatial Span; DMS, Delayed Matching to Sample; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; SRM, Spatial Recognition Memory; RVP, Rapid Visual Information Processing; RTI, Reaction Time.

Although there are relatively few published studies assessing the cognitive enhancing effects of pharmacological treatments in depression, one potential augmentation therapy is the wakefulness-promoting agent modafinil. Indeed, 4-week adjunctive treatment with modafinil was shown to improve performance on a task of executive function in currently depressed patients with only partial response to antidepressant therapy (DeBattista *et al.* 2004). However, further research is required to delineate coincidental improvements in mood and fatigue from true improvements in cognitive function.

Limitations

One limitation of the current systematic review and meta-analysis relates to lack of assessment of the association between cognitive deficits and depressive symptoms. The importance of consideration of this association was highlighted in a meta-analysis that revealed that severity of depressive symptoms correlated significantly with impairment across domains of cognition including executive function, episodic memory and processing speed (McDermott & Ebmeier, 2009). However, only a small portion (at most around 10%) of the variability in cognitive function is accounted for by variability in depressive symptom severity (McDermott & Ebmeier, 2009). Therefore, there remains considerable separation between symptoms of depressive mood and cognitive impairment in patients suffering from depression, indicating that cognitive impairment cannot be considered entirely as a secondary feature of low mood in depression. Overall, although there is some evidence of an association between depressive symptomatology and cognitive function, this association does not account for the majority

of variability in cognitive performance in depressed patients.

A further limitation of this study relates to most patients in the included studies being medicated. However, our subanalysis demonstrated significant cognitive deficits in unmedicated currently depressed patients on the SWM, DMS, PRM and RVP tasks, which span the domains of executive function, memory and attention. These findings support the idea that cognitive impairment is at least in part separable from medication effects in currently depressed patients.

The final limitation relates to the range of criteria used to define remission from depression within the remitted samples. Therefore, it is possible that our results may have been affected by the presence of low levels of persisting depressive symptoms in the remitted depressed group.

Conclusions

This review has demonstrated that cognitive impairment across the domains of executive function and attention, and to an extent memory, represents a core and clinically relevant feature of depression that persists beyond symptoms of low mood. Cognitive impairment is exhibited by depressed patients during current and remitted states, including in unmedicated samples. Previous research has demonstrated that cognitive impairment cannot be fully accounted for by severity of depressive symptoms and, along with symptoms of low mood, is associated with poor psychosocial function. We argue that cognitive impairment may represent a valuable target for new therapies for depression because remediation of cognitive impairment in addition to depressive symptoms will be important in improving functional outcome for patients with depression.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291713002535.

Declaration of Interest

Drs Rock, Riedel and Blackwell are full-time employees of Cambridge Cognition, and Dr Blackwell holds shares in Cambridge Cognition. Dr Roiser is a paid consultant for Cambridge Cognition.

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K161328/S001

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December 21, 2016

Traditional 510(k)
Submission
Deficiency Letter Response
K161328

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

RE: Original 510(k) – CANTAB Mobile, K161328
Deficiency Letter Response – Additional Information Amendment

ATTN: Binoy Mathews

Dear Sir or Madam:

Reference is made to the Division's Deficiency Letter dated July 15, 2016, which describes the Division's queries and concerns with CANTAB Mobile's original 510(k) submission dated May 10, 2016. Cambridge Cognition Ltd. responds to the request for additional information by submitting updated versions of previously submitted documents as well as new content. For ease of review, each deficiency list item is listed directly below in the Contents of Submission and also in tabular format listing each deficiency item and the corresponding Sponsor response.

CANTAB Mobile is a software application intended to be used to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years. Along with the memory test, there are optional mood and functional assessments which can help detect symptoms of depression (Geriatric Depression Screening Questionnaire [GDS]), and

problems with performing regular activities of daily living (Activities of Daily Life Questionnaire [ADL]).

CANTAB Mobile is not a diagnostic test. A diagnosis can only be made by a qualified physician using consensus diagnostic criteria. The option to test or not to test is a decision that rests with the medical professional.

The content in this 510(k) submission has been amended to support the claim that CANTAB Mobile is substantially equivalent to the previously approved predicate device, Cognivue (manufactured by Cerebral Assessment Systems, Inc.; DEN130033). CANTAB Mobile and Cognivue are both categorized as Computerized Cognitive Assessment Aid and both are used by healthcare professionals to measure aspects of patients' cognition. In addition, CANTAB Mobile and Cognivue are similar in terms of technological characteristics as both electronically record objective performance measurements when the patient responds to stimuli presented on the screen. Differences in the design and performance of CANTAB Mobile and Cognivue do not affect either the safety or effectiveness of CANTAB Mobile for its intended use.

The documents included in this submission (both paper and electronic formats) have been formatted in accordance with the *Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)* and listed on the attached page entitled "Contents of Submission". The eCopy submission is an exact duplicate of the paper copy except for the electronic-only content specified in the Contents of Submission footnotes. For ease of review, these format-specific statements are consolidated here and present in both the eCopy and paper copy.

If you have any questions, please do not hesitate to contact me at the telephone or email address listed directly below:

Sincerely,

Nancy Clementi

Nancy D. Clementi, MD
Chief Medical Officer
US Agent for Cambridge Cognition Ltd.

Encl: FDA Form 3514, Contents of Submission

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December 21, 2016

Traditional 510(k)
Submission
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K161328

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10903 New Hampshire Avenue
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If you have any questions, please do not hesitate to contact me at the telephone or email address listed directly below:

Sincerely,

Nancy Clementi

Nancy D. Clementi, MD
Chief Medical Officer
US Agent for Cambridge Cognition Ltd.

Encl: FDA Form 3514, Contents of Submission

Contents of Submission: 510(k) CANTAB Mobile[1]

Deficiency Letter Response – Additional Information Amendment 1

1 Document signature pages are available upon request.
2 Updated or amended document
3 New Document
4 Only newly submitted key references are included in the electronic submission. Please refer to the Original CANTAB Mobile 510(k) submission (10-May-2016) for other references listed.
5 The majority of references present in the IFU are included electronically in either the Executive Summary (Section 10 of original submission) or Device Description (Section 11 of original submission). All other references are available upon request.
6 References are available upon request.
7 This document is available in the electronic version of the submission. It resides in the statistical data folder in its native.xml format (zipped). A PDF version is present in Volume 5 (Item 6 Response).

Tabular Listing of Deficiency Letter Item and Corresponding Sponsor Response

Product Name: Cantab Mobile (K161328)

Indication: Assess Memory by Testing Visuospatial Associative Learning in Patients Aged 50 to 90 Years

Sponsor

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Item #	FDA Deficiency Description and Sponsor Response
Substantial Equivalence Discussion #1	**FDA Comment:** *"You have identified the AnthroTronix – DANA (K141865) as the primary predicate device for comparison to the Cantab Mobile for the purposes of establishing substantial equivalence. The DANA indications for use state that it "provides clinicians with objective measurements of reaction time (speed and accuracy) to aid in the assessment of an individual's medical or psychological state. DANA also delivers and scores standardized psychological questionnaires"). In comparison, the Cantab Mobile seeks to be indicated "for the assessment of memory in adult individuals aged 50 to 90 years of age." The device also specific in that it is "indicated to provide clinicians with objective measurements of visuospatial episodic memory and mood."* *Reaction Time and Memory are two distinct cognitive processes which are used to assess different aspects of cognition. Therefore, the predicate device you have chosen is not appropriate. Please select a predicate device whose intended use is similar to the Cantab Mobile and revise your application accordingly. We believe it is appropriate for you to consider using DEN130033 (Cerebral Assessment Systems, Inc. – Cognivue) or K150154 (Vista Lifesciences – ANAM Test System) as potential predicate devices as these devices are indicated as computerized adjunctive assessments of memory. However, please note that you will need to provide a detailed comparison to the new predicate device, and where differences exist, information to support how Cantab Mobile can be considered equivalent. For example, while considering these predicates please keep in mind that these testing systems use multiple tests to produce an outcome; you would need to support the use of the PAL as a single test used to assess memory in comparison to these predicates which test memory in multiple domains. Additionally, it is important to provide evidence that the PAL may be used without an assessment of baseline function in the proposed use and that decrements cited as severe are outside the range that could attributed to normal aging."* **Sponsor Response:** Per the Division's recommendation above, the Sponsor has updated the predicate device for comparison to Cognivue. The **Executive Summary** (**Section 5.1** and **Appendix A**) as well as **CDRH Premarket Review Submission Cover Sheet, FDA Form 3514** have been updated to reflect this change and are submitted herein.

Indications for Use #2	*"Your Indications for Use Statement states that the Cantab Mobile will be used to assess memory in patients aged 50 to 90 years. The assessment of memory is a broad term and your Indications for Use should specify the type of memory that is being assessed in order to provide the user with an accurate description of the purpose of the device. Since the Cantab Mobile will use the PAL test to make its assessment of visuospatial learning, please revise your Indications for Use Statement to "assess visuospatial associative learning in patients aged 50 to 90 years."* **Sponsor Response:** The **Indications for Use statement (FDA Form 3881)** has been revised in accordance with the Division's recommendations. All documents containing this statement have been updated and are resubmitted in this amendment.
Device Description #3	**FDA Comment:** *"Within your Executive Summary and Device Labeling, you make multiple references to specific conditions such as Mild Cognitive Impairment and Dementia and state that the Cantab Mobile can detect memory impairment in such individuals. Please note that indicating your device for "assessment of memory in adult individuals aged 50 to 90 years of age" is different from making claims related to specific disease states; test scores resulting in this outcome may be attributed to other causes and patients should be referred for clinical evaluation. Indicating your device for MCI or Dementia would constitute a new intended use which would need to be reviewed via the DeNovo pathway due to lack of a suitable predicate. Therefore, please revise your Executive Summary, Device Results, and labeling by removing the reference to MCI or Dementia. In addition, please include a statement that the results of the Cantab Mobile should only be interpreted by a qualified professional."* **Sponsor Response:** The Sponsor has ensured that any references to Mild Cognitive Impairment and Dementia are contained only in reference to peer-reviewed publications where PAL has been used to assess these conditions in a research context. It is not claimed that Cantab Mobile can detect memory impairments in specific disease states. The Sponsor includes a statement in the **Executive Summary (Section 2)** and (b) (4) "CANTAB Mobile is not a diagnostic test. A diagnosis can only be made by a qualified physician using consensus diagnostic criteria."

#4	**FDA Comment:** *"You state that the Cantab Mobile includes the optional administration of the Geriatric Depression Screening Questionnaire (GDS) and the Activities for Daily Living Questionnaire (ADL). If administered, you mention that scores will be presented to the clinician. Please address the following items related to these questionnaires:"* **FDA 4a Comment:** (b)(4) **Sponsor 4a Response:** (b)(4) **FDA 4b Comment:** *"4b. In addition, please verify if the GDS and ADL Questionnaires are consistent with the published, validated versions. If not, please cite the versions used and provide literature to support their clinical use."* **Sponsor 4b Response:** **Device Description Section 1.3** provides references to the validation of the versions of GDS and ADL used in Cantab Mobile.

	FDA 4c Comment: (b)(4) **Sponsor 4c Response:** (b)(4)
#5	**FDA Comment:** (b)(4) **Sponsor Response:** (b)(4)
#6[a]	**FDA Comment:** (b)(4) **FDA 6a Comment:** (b)(4)

(b) (4)

Sponsor 6a Response:

(b)(4)

(b)(4)

FDA 6b Comment:

(b)(4)

Sponsor 6b Response:

(b)(4)

(b)(4)

(b) (4) Testing

FDA 6c Comment:

(b)(4)

Sponsor 6c Response:

Verification and Validation testing

(b) (4) Testing

Additional information is provided in **Response to Deficiency Item 6c: Cantab Mobile Verification and Validation.**

Test-retest reliability

(b) (4) Testing

Software #7	(b)(4)
	Sponsor Response: (b) (4)

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Form Approved: OMB No. 0910-0616. Expiration Date: 2/28/2018. See PRA Statement on page 2.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance

Under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. Name of Sponsor/Applicant/Submitter
Cambridge Cognition Ltd. US Agent: Clementi Associates Ltd.

2. Date of the Application/Submission Which This Certification Accompanies
12/21/2016

3. Address

Address 1 *(Street address, P.O. box, company name c/o)*
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4. Telephone and Fax Numbers *(Include country code if applicable and area code)*
(Tel): (610) 527-2600
(Fax): 215-717-4698

PRODUCT INFORMATION

5. **For Drugs/Biologics:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s).
For Devices: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)

CANTAB Mobile

Continuation Page for #5

APPLICATION / SUBMISSION INFORMATION

6. Type of Application/Submission Which This Certification Accompanies

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. Include IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/ Other Number *(If number previously assigned)*
161328

If BLA was selected in item 6, provide Supplement Number

8. Serial Number Assigned to Application/Submission Which This Certification Accompanies
00001

CERTIFICATION STATEMENT / INFORMATION

9. Check only one of the following boxes *(See instructions for additional information and explanation)*

☒ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

Certification Statement / Information section continued on page 2

CERTIFICATION STATEMENT / INFORMATION *(Continued)*

10. If you checked box C, in number 9, provide the National Clinical Trial (NCT) Number(s) for any "applicable clinical trial(s)," under 42 U.S.C. § 282(J)(1)(a)(i), section 402(j)(1)(a)(i) of the Public Health Service Act, referenced in the application/ submission which this Certification accompanies. *(Add continuation page as necessary.)*

NCT Number(s): _____ _____ _____ _____ _____

Continuation Page for #10

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.

Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. Name and Title of the Person who Signs Number 15

Name	Title
Nancy D. Clementi, M.D.	Chief Medical Officer, Clementi Associates Ltd.

12. Address

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14. Date of Certification

12/21/2016

15. Signature of Sponsor/Applicant/Submitter or an Authorized Representative *(Sign)*

Sign

Nancy D Clementi

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10. Executive Summary

Product Name: Cantab Mobile (K161328)

Indication: Assess Memory by Testing Visuospatial Associative Learning in Patients Aged 50 to 90 Years

Sponsor

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale – Cognition
ADHD	Attention deficit hyperactivity disorder
ADL	Activities for Daily Living Questionnaire
CANTAB	Cambridge Neuropsychology Test Automated Battery
CAPA	Corrective and Preventative Action
DLB	Dementia with Lewy Bodies
FDS	Functional Design Specification
GDS	Geriatric Depression Screening Questionnaire
HD	Huntington's disease
ID	Identification
IFU	Instructions for Use
MCI	Mild Cognitive Impairment
MEDDEV	Medical Device guidance document
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association
PAL	Paired Associates Learning
PIN	Personal Identification Number
RS	Requirements Specification
SCM	Software Configuration Management
SDLC	Software Development Life Cycle
SDS	Software Design Specification
SOP	Standard Operating Procedure
SOUP	Software Of Unknown Provenance
QD	Questionable dementia
QMS	Quality Management System
VMP	Validation Master Plan

1 BACKGROUND

1.1 Information on Dementia and Relevancy of Testing

It is estimated that dementia currently affects approximately 37 million people worldwide and, as the population ages, these prevalence rates can be expected to increase substantially. In addition to the devastating personal impact that a diagnosis of dementia may have upon the lives of patients and their caregivers, there is also a financial burden. The total monetary cost of dementia in 2010 was between $157 billion and $215 billion (Hurd et al., 2013).

Current criteria for the diagnosis of probable AD stipulates deterioration in two or more areas of cognition including memory of sufficient magnitude to interfere with work or social function. Critically however, substantial neuropathological change may have occurred before clinically significant symptoms (Jack et al. 2010; Jansen et al. 2015) appear. Thus, commencing treatment of AD at the time of clinical diagnosis (whether with cholinergic / glutamatergic drugs, anti-amyloid deposit agents or other putative disease modifying agents) may be sub-optimal or even ineffective because of the advanced stage of neurodegeneration at that time. The identification of cognitive tests that are sensitive to early pathological changes would facilitate the diagnosis of patients in a 'prodromal' state (i.e., those in whom the pathological process is present but whose symptoms are currently sub-clinical). Such early detection would serve to maximize the potential therapeutic benefit of treatment, enhance patient quality of life and, in so doing, reduce the burden on residential and nursing care services. Consequently, a very high therapeutic and economic premium is placed on the early detection and diagnosis of AD.

The CANTAB (Cambridge Neuropsychology Test Automated Battery) PAL (Paired Associates Learning) requires patients to learn and remember abstract visual patterns associated with various locations on a touch sensitive computer screen. See Device Description Section 1.2 for additional detail.

A series of independent studies have demonstrated that Cantab PAL measures of visuospatial associative learning and semantic memory are sensitive in detecting the earliest signs of prodromal Alzheimer's disease (up to 32 months prior to clinical diagnosis) both in memory clinic attendees (Fowler et al., 1995, Fowler et al., 1997; Fowler et al., 2002; Swainson et al., 2001; Blackwell et al., 2004) and in community dwelling cohorts of individuals classified as asymptomatic using current clinical measures (De Jager et al., 2002); De Jager et al., 2005).

Further studies using Cantab PAL have confirmed it to be of utility in early and differential diagnosis in AD on a case-by-case basis. The Cantab PAL performance of patients with mild AD was impaired relative to both demographically-matched healthy controls (Sahakian et al., 1988) and to individuals with Frontal Variant Fronto-Temporal Dementia (Lee et al, 2003). Of critical importance, Cantab PAL was also found to be relatively insensitive to major unipolar depression (only 7 percent of scores of patients with Depression and Alzheimer's disease fell within an overlapping range) (Swainson et al., 2001). This result suggests that Cantab PAL is of utility in the differential diagnosis of early AD and depression (unlike word recall tests – see O'Carroll et al., 1997). Unlike ADAS-COG, performance on Cantab PAL

was also found to correlate significantly with subsequent deterioration in global cognitive function. Furthermore, in a group of individuals with 'questionable dementia', baseline Cantab PAL results revealed an apparent subgroup of patients who performed like AD patients. In a follow up study, Blackwell et al. (2004) showed that by taking into account age and performance on one other neuropsychological test (The Graded Naming Test [McKenna & Warrington, 1980]), Cantab PAL gave a 100% distinction between patients with questionable dementia who either did or did not convert to probable AD (NINCDS-ADRDA criteria) 32 months after baseline testing (see also De Jager et al., 2002). These studies also revealed that the sensitivity (in detecting prodromal AD in a QD group) and specificity (in differentiating AD from depression) of Cantab PAL was considerably better than that of all other frequently-used tests included in the study (including ADAS-cog and Wechsler Logical Memory Delayed Passage Recall).

The accumulating evidence demonstrates the sensitivity and specificity of Cantab PAL as a tool for operationalizing the criteria for objective memory impairment in mild cognitive impairment (MCI).

2 INDICATION(S) AND INTENDED USE

The application is designed to detect episodic memory impairments in patients aged 50 to 90 years by testing visuospatial associative learning (Table 1). Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression (Geriatric Depression Screening Questionnaire [GDS]), and problems with performing regular activities of daily living (Activities of Daily Life Questionnaire [ADL]). Additional information on questionnaires is provided in the amended Device Description (Vol. 3).

Table 1. Indications for Use

Indications for Use	The device is intended to be used to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years.
Contraindications	Patients with severe visual impairment Patients outside the indicated age range

The results of Cantab Mobile should be interpreted only by qualified professionals. The application provides test results that are interpretive, however, Cantab Mobile is not a diagnostic test. The output provided by the device is not diagnostic. A diagnosis can only be made by a qualified physician using consensus diagnostic criteria. The option to test or not to test is a decision that rests with the medical professional.

2.1 Instructions for Use

The Instructions for Use (IFU) is included as a separate document in this submission. Please see **NMI-013** for the full Instructions for Use for Cantab Mobile.

3 DEVICE DESCRIPTION

A full **Device Description** is included as a separate document in this submission

3.1 Summary

Cantab Mobile is software to be loaded and run on Apple iPad hardware and operating system. The software is intended to be administered by a healthcare professional to test the cognitive function of a patient. The Cantab Mobile memory test is based on the Cantab PAL test, which requires patients to learn and remember abstract visual patterns associated with various locations on a touch-sensitive computer screen. Two optional questionnaires are included to assess a patient's mood and ability to perform daily living activities. At the conclusion of the test, a 'thank you' screen is displayed with no information on test outcome. The healthcare professional will then be able to read or export a report, which summarizes the memory test results and also displays information on the patient's responses in the questionnaires, if these have been administered.

Cantab Mobile has been classified as a Class I Medical Device in accordance with:

- MEDDEV 2.1/6 – July 2016
- 93/42/EEC on Medical Devices, Classification Criteria, Annex IX, Rule 12.

The proposed regulatory classification, made under this 510(k) submission, is Class I. It is a Computerized Cognitive Assessment Aid (Product Code PKQ) and the classification regulation number is CFR 882.1470. Appendix A presents supportive information for this classification designation.

4 VERIFICATION, VALIDATION AND TRACEABILITY

Software development is carried out under a controlled Software Development Life Cycle within a Quality Management System. A summary of the current version of these procedures in relation to IEC 62304:2006 for Class A software systems is provided in **QA-IEC62304Analysis.** **The Software Section** of this submission provides additional supportive information.

Version 1.4 is the current version of the application. The history of prior application changes and verification is reflected in the **Summary Table in the Software Section.**

In addition to the traceability of verification records and risk control activities provided in the above documents, traceability between requirements, functional design and software testing specifications is summarized in **NMI-018.**

Functional testing is conducted against controlled software versions using a defined test specification, which documents the criteria required for each test case to pass; the pass/fail outcome for each case is recorded in records of testing for the software version.

A revision history log of external software releases with version identification is maintained under the control of the software configuration management system.

5 SUBSTANTIAL EQUIVALENCE

5.1 Predicate Device

Cantab Mobile is substantially equivalent to Cognivue (manufactured by Cerebral Assessment Systems; DEN130033). Cantab Mobile and Cognivue are both categorized as Computerized Cognitive Assessment Aids. The tests use different devices; Cantab Mobile uses an Apple iPad and Cognivue uses a personal computer on a cart. Cantab Mobile and Cognivue are both used by healthcare professionals to measure aspects of patients' cognition. Cantab Mobile and Cognivue differ in the areas of cognition measured in that Cantab Mobile specifically assesses memory using a test of visuospatial associative learning (PAL) that is known to be correlated with hippocampal function, whereas the Cognivue software gives an overview of brain health, including memory, using ten short tests.

The results of the PAL test in Cantab Mobile are automatically compared to the results in the built-in normative dataset, accounting for age, gender and level of education, to indicate when a patient's memory is outside the range that could be attributed to normal aging. This is designed to be a triage test for people with concerns about their memory, to determine whether a patient should be tested further or their memory is normal for their age. Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living. Cognivue is designed to be used to regularly monitor a patient's broad cognitive health, using 10 short tests to indicate decline, and potentially dementia, through comparison to baseline test performance of other age-normal adults.

Cantab Mobile and Cognivue are similar in terms of technological characteristics as both electronically record objective performance measurements when the patient responds to stimuli presented on the screen. Differences in the design and performance of Cantab Mobile and Cognivue do not affect either the safety or effectiveness of Cantab Mobile for its intended use.

Table 2 presents a summary of each device for comparison. A complete comparison table is provided in Appendix A.

Table 2. Device Comparison Summary (Proposed Device vs. Predicate Device)

Comparison Items	**CANTAB Mobile- Cambridge Cognition Ltd.**	**Cognivue – Cerebral Assessment Systems, Inc.** (Submitted June 26, 2013)
510(k) Number	K161328	DEN130033
Trade Name	Cantab Mobile	Cognivue
Regulation Name:	Computerized Cognitive Assessment Aid	
Intended Use	Cantab Mobile is intended to be used to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years. Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living. Results should be interpreted only by qualified professionals. The device is not intended to be used as a stand-alone diagnostic device. The device is not intended to identify the presence or absence of clinical diagnoses.	Cognivue testing is indicated as an adjunctive tool for evaluating perceptual and memory function in individuals aged 55 to 95 years old. Results should be interpreted only by qualified professionals. The device is not intended to be used as a stand-alone diagnostic device. The device is not intended to identify the presence or absence of clinical diagnoses.

(b)

7 RISKS TO HEALTH

7.1 Summary

Risk management for the device is handled under controlled procedures within a Quality Management System. These procedures are designed to meet applicable requirements of EN ISO 13485:2012 and EN ISO 14971:2012.

A summary of the risk analysis and other document references are provided in the **Device Description (Section 2.2)**.

7.2 Determination of Level of Concern

Cantab Mobile's level of concern is classified as minor based upon the parameters and recommendations outlined in FDA's *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (2005), with negative responses to all questions in Tables 1 and 2. Regarding question 3 in Table 2, the app is a screening device for use by a learned intermediary in conjunction with other investigations; its operation does not lead directly to diagnosis or choice of appropriate medical care.

8 OVERALL CONCLUSIONS

Cantab Mobile is an app that runs on an iPad. It detects memory impairments by testing visuospatial associative learning, in patients aged 50 to 90 years, and includes optional mood and functional assessments which can help detect symptoms of depression and problems with performing regular activities of daily living. The Cantab tests have a 30-year history of use in a range of clinical populations, supported by over 1500 published papers. Cantab Mobile includes the Cantab PAL test, which has been developed as a way of assessing episodic memory without language barriers. A series of independent studies have demonstrated that PAL is sensitive in detecting the earliest signs of prodromal Alzheimer's disease, up to 32 months prior to clinical diagnosis, and that it is relatively insensitive to major unipolar depression. The accumulating evidence demonstrates the sensitivity and specificity of PAL as a tool for operationalizing the criteria for objective memory impairment in mild cognitive impairment (MCI).

Cantab Mobile is not a diagnostic test. The results for a patient's PAL memory test are presented to the healthcare professional as one of three traffic-light coded categories. In conjunction with other investigations, these provide information to assist the professional in their assessment of the patient.

Cantab Mobile is substantially equivalent to Cerebral Assessment Systems' Cognivue software in that they share the intended use of providing clinicians with objective measurements of cognition. Both are applications that electronically record objective performance measurements as the patient responds to stimuli presented on the screen. Differences in the design and performance of Cantab Mobile from Cognivue, the predicate device, do not affect either the safety or effectiveness of Cantab Mobile for its intended use.

9 LITERATURE CITED

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Swainson R, Hodges JR, Galton CJ, Paykel ES, Semple J, Michael A, et al. Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. Dement Geriatr Cogn Disord. 200;12(4):265-80.

10 APPENDICES

Appendix A. Predicate Device Comparison (Cantab Mobile and Cognivue)

Comparison Items	**CANTAB Mobile- Cambridge Cognition Ltd.**	**Cognivue – Cerebral Assessment Systems, Inc.**
510(k) Number	K161328	DEN130033
Device Information: Trade Name	Cantab Mobile	Cognivue
Regulation Name:	Computerized Cognitive Assessment Aid Classification Regulation # CFR 882.1470	Computerized Cognitive Assessment Aid Classification Regulation # CFR 882.1470
Product Code	PKQ	PKQ
Device Information: Device Class:	Unclassified or Proposed Class I The device has the same intended use, and relies on technology that does not raise new safety and effectiveness questions to Cognivue.	Class II
Predicate Device:	Cognivue (DEN130033)	*De novo* submission
Type of Use	Prescription Use (Part 21 CFR 801.109)	Prescription Use (Part 21 CFR 801.109)
Submission Date:	May 12, 2016	June 26, 2013
Submitter Information: Company:	Cambridge Cognition Limited. Tunbridge Court, Tunbridge Lane Bottisham Cambridgeshire, CB25 9TU UK	Cerebral Assessment Systems, Inc. 2850 Clover Street Pittsford, NY 14534 USA
Design and Intended Use	Cantab Mobile is intended to be used to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years. Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living. Results should be interpreted only by qualified professionals. The device is not intended to be used as a stand-alone diagnostic device. The device is not intended to identify the presence or absence of clinical diagnoses.	Cognivue testing is indicated as an adjunctive tool for evaluating perceptual and memory function in individuals aged 55 to 95 years old. Results should be interpreted only by qualified professionals. The device is not intended to be used as a stand-alone diagnostic device. The device is not intended to identify the presence or absence of clinical diagnoses.

Comparison Items	**CANTAB Mobile- Cambridge Cognition Ltd.**	**Cognivue – Cerebral Assessment Systems, Inc.**
Target population	Patients aged 50 to 90 years with concerns about their memory. Results are automatically adjusted for age, gender, education.	Patients aged 55 to 95 years for the purpose of identifying a potential decline in cognitive function relative to baseline test performance of other age-normal adults.
Anatomical site	The brain: cognitive function	The brain: cognitive function
Test duration	The test takes approximately 10 minutes to complete.	The test takes approximately 10 minutes to complete.
Scoring and reports	Automatic scoring and instant reports	Automatic scoring and instant reports
Where used	Cantab Mobile is software used on a tablet, therefore it can be administered in any suitable setting, e.g. a clinic or home.	The Cognivue software is used on a personal computer, situated on a cart to provide mobility within the healthcare setting.
Energy used	Cantab Mobile software runs on an Apple iPad, which has the following features: ▪ built-in 25-watt-hour rechargeable lithium-polymer battery; ▪ charging via power adapter or USB to computer system; ▪ up to 10 hours of use when charged.	The Cognivue software runs on a personal computer – the energy used is hardware-dependent.
Human factors	Any healthcare professional can administer the test. To ensure reliable results, the iPad should be placed on a stand and the assessment should be administered in a quiet room, without disturbance. The voiceover and questionnaire texts are provided in a choice of languages.	Any healthcare professional can administer the test. The battery is organized into three sub-batteries, with each sub-test preceded by transitional guidance that facilitates the test subject's engagement with minimal supervision.
To whom is the product marketed /target audience?	Healthcare Rehabilitation	Healthcare
Materials	N/A	N/A
Biocompatibility	N/A	N/A
Compatibility with the environment and other devices	N/A	N/A
Sterility	Based on the device function there is no sterilization testing required for this device.	Based on the device function there is no sterilization testing required for this device.

Comparison Items	**CANTAB Mobile- Cambridge Cognition Ltd.**	**Cognivue – Cerebral Assessment Systems, Inc.**
Safety: electrical; mechanical; chemical; thermal; radiation.	These safety issues are not applicable to this software-only device.	Electrical safety testing was performed by Canadian Standards Association. The sponsor provides a letter of attestation stating the device passed IEC 60601-1:2005. Electromagnetic compatibility was not tested.
How the device differs from Predicate device	Cantab Mobile is similar to Cognivue in terms of technological characteristics, as both electronically record objective performance as the patient responds to stimuli presented on the screen. Both tests take about 10 minutes. Cantab Mobile differs from Cognivue in that it provides an assessment of memory using one staged cognitive assessment – the Paired Associates Learning task - compared to Cognivue which includes ten short brain function tests, measuring: adaptive motor control; dynamic visual contrast sensitivity; letter, word, shape, and motion processing ability; and memory. Cantab Mobile also presents assessments of depression and activities of daily living, which are not included in Cognivue.	

11 REFERENCED DOCUMENTS

Traceability Matrix (NMI-018)[1]

Change Control and Validation Report (CR-NMI-004)

(b) (4)

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11. DEVICE DESCRIPTION

Product Name: Cantab Mobile (K161328))
Indication: Assess Memory by Testing Visuospatial Associative Learning in Patients Aged 50 to 90 Years

Sponsor

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1 DEVICE DESCRIPTION

Cantab Mobile is software to be loaded and run on Apple iPad hardware and operating system (Figure 1). Below is a list of possible device accessories:

- The iPad[1] is an essential accessory
- Disposable iPad Sleeve (see also **Instructions for Use**) for cleaning recommendations)
- iPad stand
- A iPad battery charger is also supplied with the iPad

Figure 1. iPad with App Icon at Top Left

Cantab Mobile does not have a restricted shelf-life. Ongoing support of the manufacturer is required, however, and is detailed below.

The medical device software must be updated when new releases are made available. The iPad operating system should also be kept up to date. Both may be achieved automatically. The iPad battery should be charged as required. No calibration is necessary.

Ongoing support by the manufacturer is required. The app must be able to confirm periodically with the manufacturer that it is licensed, and be updated as required over time.

1 Cantab Mobile is not authorized for use on the iPad mini or the iPad 1 (the first generation iPad). Do not install the app on these devices.

The test is not susceptible to environmental influences within the defined environment for its administration. We instruct that physicians must always administer the tests in a quiet, peaceful environment, with the iPad volume level set so that the patient can clearly hear instructions being given. For patients with impaired hearing, additional support may need to be provided to ensure they can correctly hear and understand the instructions during the test, e.g. use headphones.

A technical wireframe, or mobile app screen blueprint, of Cantab Mobile is a supportive document that presents the skeletal framework, interface elements, and navigational flow (See **Cantab Mobile Wireframes**).

1.1 Patient Data Entry

Prior to the PAL test itself, the healthcare professional administering the test enters patient data (patient ID, date of birth, gender, educational background etc.).[2] This is used in assessing the patient's performance against a set of normative data.

Figure 2. Data Entry Screen

1.2 Memory Test

Cantab Mobile provides an optional patient self assessment of memory (Self Assess - enabled on the data entry screen). If this assessment is enabled, the patient will rate his/her memory prior to taking Cantab PAL. The patient is presented a rating scale against which they rate their memory as above average (left of center), average (center), or below average (right of center) (See Appendix A). Comparing self-rated memory with the objective

2 Patient details must be entered correctly. Incorrect patient details can lead to incorrect reporting of patient impairment.

measure of memory, provided by Cantab PAL, can reveal any discrepancies between actual and perceived memory ability.

The Cantab Mobile memory test is based on the Cantab PAL test previously used on other hardware platforms. The Cantab PAL requires patients to learn and remember abstract visual patterns associated with various locations on a touch-sensitive computer screen. The patterns were all created to be bold, brightly colored, abstract and with no cultural context
See Appendix B for examples of patterns used.

Patterns are presented in six boxes around the edge of the screen (See Figure 3). The patterns disappear from the screen, leaving empty boxes and, after a brief delay, the same patterns are presented sequentially in the middle of the screen and the patient is required to touch the box in which they previously saw that pattern appear. (Figure 4)

Figure 3. Pattern Appears in Box

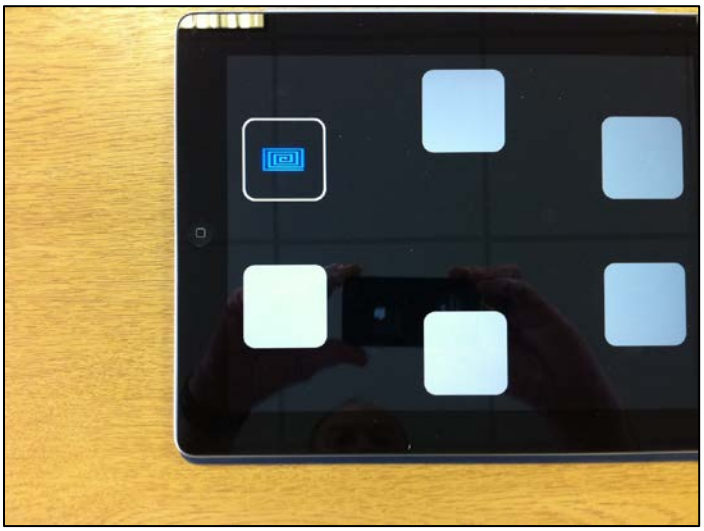
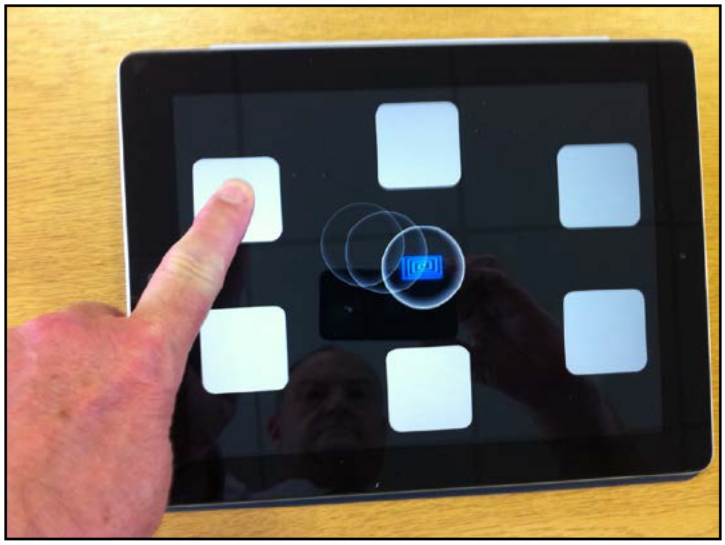


Figure 4. Patient Chooses Box



If the patterns' locations are not recalled correctly, this is identified to the patient via audio prompts and pattern presentation and recall is repeated. This process continues until the task is completed successfully, at which point the next task is started, or repeated failures by the patient to recall the locations correctly cause the test to end. The whole test consists of a series of such tasks with increasing levels of difficulty.

The patient's responses are recorded by screen touches. The number of errors that they make are recorded and their performance is graded using algorithms derived from a normative database(b) (4)

1.3 Questionnaire(s)

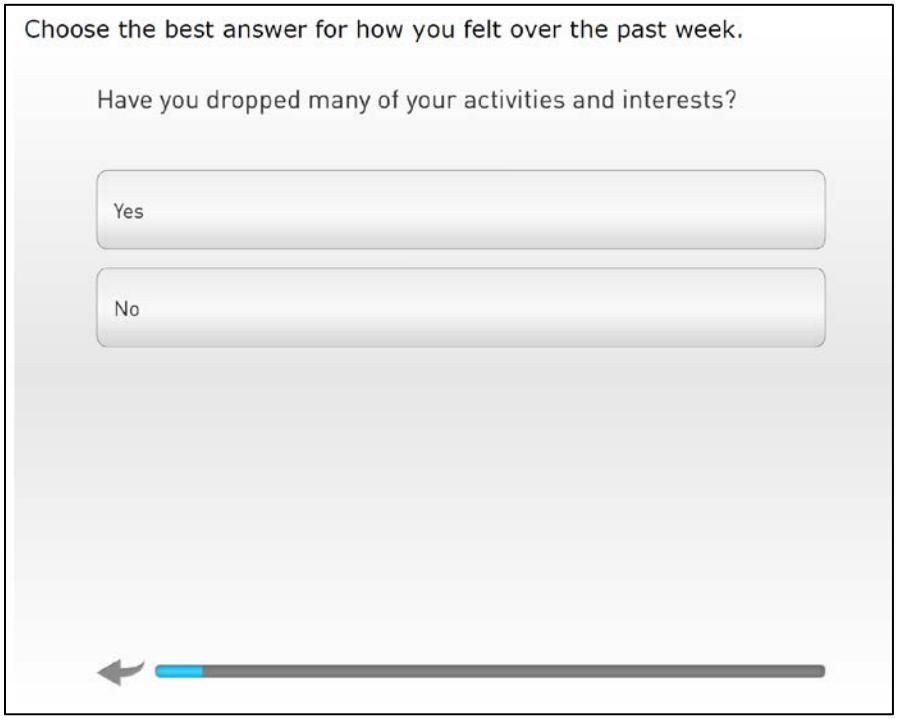
Cantab Mobile additionally includes optional questionnaires. Questionnaires operate by presenting a series of questions to the patient, with clearly labeled response boxes that the patient may touch in order to answer each question (Figure 5). Ratings scales administered (depending on patient performance – see Appendix D – and if not disabled by the healthcare professional) comprise:

1. GDS – Geriatric Depression Screening Questionnaire (See Appendix C)
2. ADL – Activities for Daily Living Questionnaire (See Appendix D)

The GDS rating scale in the app is the shorter version of GDS including 15 questions, the GDS-15 (validated by Almeida and Almeida 1999), which is based on the GDS described by Yesavage and colleagues (Yesavage et al 1983): The GDS rating scale comprises a series of questions, each presented in turn textually on the screen using the language in force, two buttons below to allow the patient to respond 'yes' and 'no' (or equivalent in the language in force). A progress bar gives an approximate indication of progress through the questions and

a button with a backward arrow allows the user to return to the preceding question (if any) and choose again. See Figure 5 below for an example of a GDS-15 rating scale question and its format, as it is presented in the app.

Figure 5. GDS Rating Scale and Format



The ADL rating scale in the app was developed and validated by Galasko and colleagues (Galasko et al 2006) with the goal of simplifying the assessment of this domain for primary prevention trials of Alzheimer's disease. The 15 items they selected for the questionnaire cover a broad range of activities, which are performed regularly by elderly individuals. Administration of the ADL rating scale comprises a series of questions, each presented in turn textually on the screen using the language in force[3], with the introductory text given above the question and buttons below to allow the patient to choose from the responses permitted for the question. A progress bar gives an approximate indication of progress through the questions and a button with a backward arrow allows (except on questions 1 and 11) the user to return to the preceding question and choose again.

3 The entire user interface respects the text direction (left-to-right or right-to-left) of the language in force including the backward arrow button and progress bar

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(b) (4)

1.5 Device Classification

Cantab Mobile is classified as a Class I Medical Device under EU directive 93/42/EEC. It is standalone software that could be regarded as allowing monitoring of vital physiological processes (MEDDEV 2.1/6 section 3.1.1).

The proposed regulatory classification for Cantab Mobile under US regulation is Class II (21 CFR 882.1470). It is a Computerized Cognitive Assessment Aid (Product Code PKQ). Device classification is covered in greater detail, in the **Executive Summary**.

(b) (4) Device Description

(b)

2.2 Device Safety Characteristics and Risks[4]

Risk management for the device is handled under controlled procedures within a Quality Management System. These procedures are designed to meet applicable requirements of EN ISO 13485:2012 and EN ISO 14971:2012.

Identification of characteristics of the device that could impact on safety are documented in **QRM-01-001**. Risk analysis was conducted according to a risk analysis plan referencing controlled procedures, namely **QRM-02-002**, and the conclusion of the risk analysis process is documented in report **QRM-02-003**.

The summary of all points of the risk analysis is provided in **QRM-02-001**.

[4] Risk Analysis documentation, cross referenced here, was previously submitted in the original 510(k) submission (dated May 11, 2016).

3 LITERATURE CITED

Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriatr Psychiatry. 1999;14(10):858-65.

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey MB, et al. Development and validation of a geriatric depression screening scale: A preliminary report. Journal of Psychiatric Research 1983;17:37-49.

Galasko D, Bennett DA, Sano M, Marson D, Kaye J, Edland SD for the Alzheimer's Disease Cooperative Study. ADCS Prevention Instrument Project: Assessment of Instrumental Activities of Daily Living for Community-dwelling Elderly Individuals in Dementia Prevention Clinical Trials. Alzheimer Dis Assoc Disord. 2006;20(Supp3):S152-69.[5]

[5] This reference was added to support the Sponsor's Response to the Division's Request for Additional Information.

(b)

(b)

Appendix C. Mood Assessment (GDS)

The Mood Assessment (GDS) is automatically administered. Cantab PAL performance is not a conditional factor in administering the Mood Assessment.

Choose the best answer for how you felt over the past week.[6]

Are you basically satisfied with your life?
☐ Yes
☐ No

Have you dropped many of your activities and interests?
☐ Yes
☐ No

Do you feel that your life is empty?
☐ Yes
☐ No

Do you often get bored?
☐ Yes
☐ No

Are you in good spirits most of the time?
☐ Yes
☐ No

Are you afraid that something bad is going to happen to you?
☐ Yes
☐ No

Do you feel happy most of the time?
☐ Yes
☐ No

Do you often feel helpless?
☐ Yes
☐ No

[6] The GDS introductory statement precedes each GDS question listed in Appendix C.

Do you prefer to stay at home, rather than going out and doing new things?
☐ Yes
☐ No

Do you feel you have more problems with memory than most?
☐ Yes
☐ No

Do you think it is wonderful to be alive now?
☐ Yes
☐ No

Do you feel pretty worthless the way you are now?
☐ Yes
☐ No

Do you feel full of energy?
☐ Yes
☐ No

Do you feel that your situation is hopeless?
☐ Yes
☐ No

Do you think that most people are better off than you are?
☐ Yes
☐ No

Appendix D. Functional Assessment (ADL)

This test is automatically administered after Cantab PAL if the patient's Cantab PAL performance has indicated that they fall in the "Investigate" category

Part 1:

In the past 3 months, were you able to:

Do your own shopping?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Prepare meals?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Write checks, pay bills, or use an ATM case machine?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Travel by car or public transport?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Carry out housework, laundry or home repairs?
☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Do hobbies such as a card games or crosswords?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Follow the story of a TV program, book or movie?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Keep track of current events in the news or the media?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Remember appointments or important dates such as birthdays?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Remember to take your medication?

☐ Yes
☐ Yes, but I had some problems or needed some help
☐ No, I could not do it
☐ I did not try

Part 2:

Can you:

See well enough to recognize someone across the street (wearing glasses or contact lenses if necessary?)

☐ Yes

☐ No

Hear what people are saying when they are speaking at a normal volume?

☐ Yes

☐ No

Walk up and down a set of stairs without help?

☐ Yes

☐ No

(b)

(b)

(b)

5 REFERENCED DOCUMENTS

Cantab Mobile Technical Wireframes[7]

Cantab Mobile Managing Reports Quick Reference Guide[8]

Demographic Adjustment of Scores (NMI-020)[7]

Identification of Characteristics (QRM-01-001)[8]

PALD Risk Management Plan (QRM-02-002)[8]

Risk Summary Report (QRM-02-003) [8]

Risk Analysis (QRM-02-001) [8]

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ORIGINAL ARTICLE

ADCS Prevention Instrument Project: Assessment of Instrumental Activities of Daily Living for Community-dwelling Elderly Individuals in Dementia Prevention Clinical Trials

Douglas Galasko, MD, David A. Bennett, MD,† Mary Sano, PhD,‡§ Daniel Marson, PhD,‖ Jeff Kaye, MD,¶ and Steven D. Edland, PhD,*; for the Alzheimer's Disease Cooperative Study*

Background: In primary prevention trials for Alzheimer disease, the inception cohort typically has normal or minimally impaired complex activities of daily living (ADL). ADL change during a trial could trigger detailed evaluation or serve as an outcome measure. A brief, easily administered, and reliable ADL rating scale would assist prevention studies.

Objectives: To develop an ADL scale for prevention trials that allows self rating or completion by informants.

Methods: The Activities of Daily Living Prevention Instrument (ADL PI) was developed, comprising 15 ADL and 5 physical function questions. Six hundred forty four elderly subjects participating in the Prevention Instrument Project completed a self rated version of the ADL PI, and informants for 632 subjects completed an informant version. Informants also completed a Mild Cognitive Impairment (MCI) ADL questionnaire to allow comparisons.

Results: Subjects performed well on all ADL scales at baseline. Completion of the ADL PI questionnaires at home or in clinic yielded comparable information. Scores from baseline to 3 months had good reliability. The ADL PI, obtained from either self report or informants, discriminated between subjects rated as CDR 0 and CDR 0.5. Subjects with worse baseline cognitive performance also had slightly worse ADL PI scores. Preliminary analysis indicates that subjects who triggered cognitive evaluations had slightly lower baseline ADL PI scores by both self and informant reports.

Conclusions: The ADL PI can be completed at home or in clinic, and has adequate reliability. The utility of self administered and informant versions and predictive value of reported deficits requires further follow up.

Key Words: activities of daily living, Alzheimer disease, clinical trial

(*Alzheimer Dis Assoc Disord* 2006;20:S152–S169)

From the *Department of Neurosciences, University of California, San Diego; †Department of Neurology, Rush Medical School, Chicago, IL; ‡Department of Neurology, Mount Sinai School of Medicine, New York; §VA Medical Center, Bronx, NY; ‖Department of Psychiatry, University of Alabama School of Medicine, Birmingham, AL; and ¶Department of Neurology, Oregon Health and Sciences University, Portland, OR.

Supported by NIA grant AG10483.

Reprints: Douglas Galasko, MD, Department of Neurosciences, University of California, San Diego, 9500 Gilman Drive No. 0624, La Jolla, CA 92093-0624 (e-mail: dgalasko@ucsd.edu).

CAMBRIDGE COGNITION

Relevant Correspondence

Sponsor's Request for Clarification

K161328: Request for Clarification of "Deficiency List" Response Letter Item #6a
(dated August 11, 2016)

"6. Within your device description you provide information on the summary report
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a. (b)(4)

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(b) (4) Copyrighted Materials

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CAMBRIDGE COGNITION

Response to Deficiency Item 6c: CANTAB Mobile Verification and Validation

SENSITIVITY TO DISEASE

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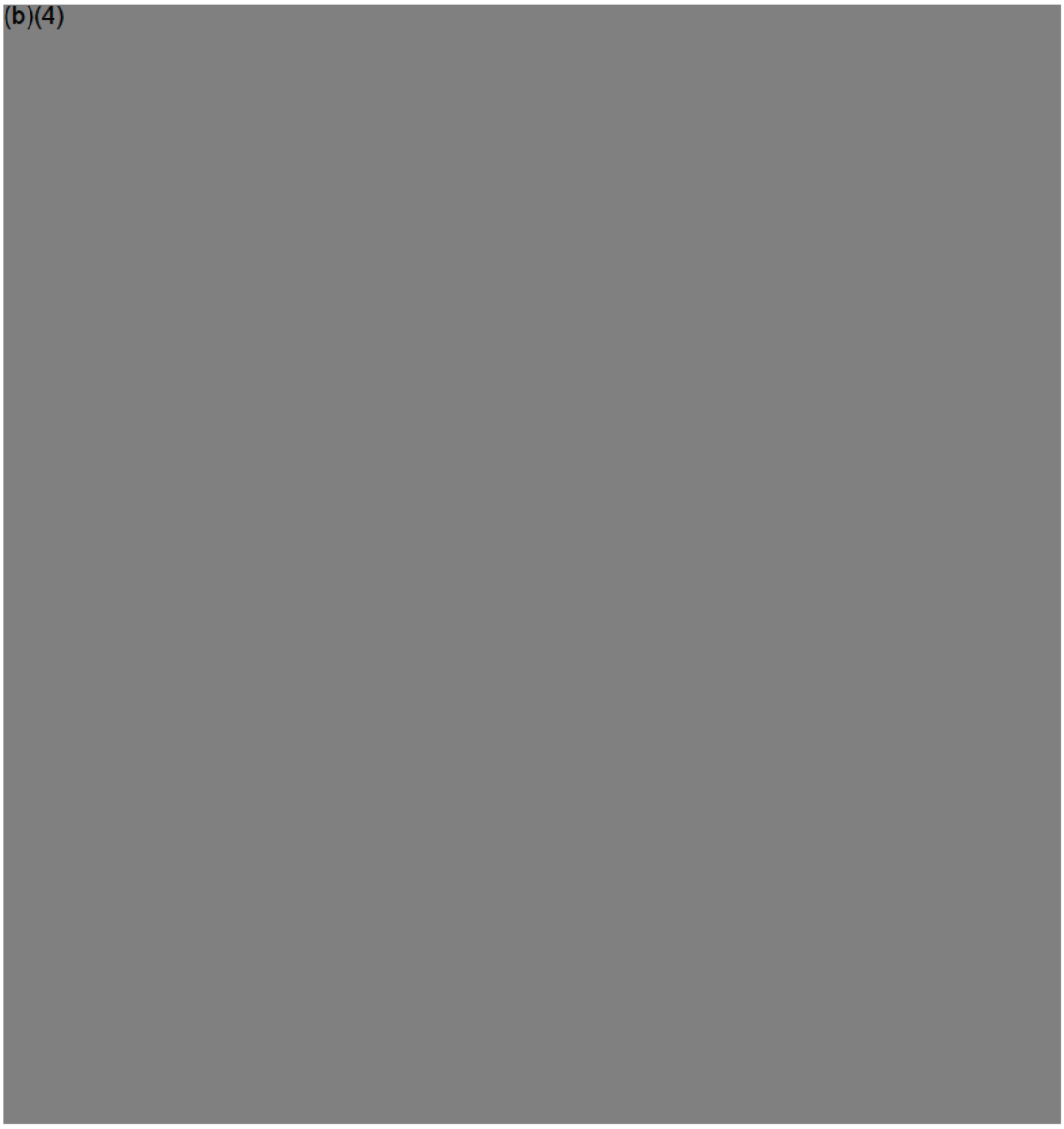

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(b) (4) Copyrighted Materials

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Exclusion Criteria:

- Other prior or current neurologic or medical disorder which may currently or during the course of the study impair cognition or psychiatric functioning
- A history of stroke
- A documented history of transient ischemic attack within the last 12 months
- History of schizophrenia, schizoaffective or bipolar disorder
- Currently meets criteria for major depression
- Within the last 2 years, unstable or clinical significant cardiovascular disease (myocardial infarction, angina pectoris)

Study C:

Inclusion criteria:

- presence of cognitive complaints (e.g. memory, attention) as reported by the participant and/or informant; preserved general cognition;
- independent daily functioning (confirmed by an informant);

Exclusion criteria:

- history of major medical, neurological or psychiatric illness (DSM-IV Axis I or II);
- history of major risk factors for vascular disease;
- history of sensory impairment or impairment to hand mobility

ASSOCIATION WITH IMAGING OF THE HIPPOCAMPUS

As a measure of episodic memory, we expect performance on this task to be associated with the integrity and function of the hippocampus, a key brain area known to subserve memory. We review some published papers describing these associations in NMI-054. Additional data has been reported from the EU ADNI project, showing an association both with hippocampal volumes and other markers of neurodegenerative change in patients with Mild Cognitive Impairment, such as the presence abnormal proteins in cerebro-spinal fluid (Nathan et al., 2015). Together these data support the dependence of the task on the hippocampus, consistent with episodic memory, and its sensitivity to pathological memory impairment such as that seen in Mild Cognitive Impairment.

Published in final edited form as:
Alzheimers Dement. 2011 May ; 7(3): 270–279. doi:10.1016/j.jalz.2011.03.008.

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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With regard to potential conflicts of interest, Marilyn Albert serves as a consultant to Genentech and Eli Lilly and receives grants to her institution from GE Healthcare. Steven DeKosky serves as a consultant to Eisai, Merck, Elan/Wyeth, Novartis, he serves on the advisory board of Pfizer and provides clinical services to United Healthcare. Dennis Dickson report no conflicts. Bruno Dubois serves as a consultant to Affiris, Pierre Fabre, and Eisai, serving on a scientific advisory board for Bristol-Meyers Squibb, Roche, Pfizer, Eli Lilly, and GE Healthcare, and receives grants to his institution from Novartis, Roche, and Eisai. Howard Feldman is an employee of Bristol Meyers Squibb (BMS) and holds stock in BMS; he serves as a consultant to Servier, Glia Scientific, and Pfizer, and serves on a scientific advisory board for Elan, Janssen, Canada, and Wyeth. Nick Fox serves as a consultant (payment to Institute of Neurology) for BMS, Elan/Janssen, Eli Lilly, GE, Lundbeck, and Pfizer/Wyeth. The Institute of Neurology (Nick Fox) has conducted image analysis for Elan/Janssen, Lundbeck, and Pfizer/Wyeth. Anthony Gamst reports no conflicts. David Holtzman serves as a consultant for Bristol-Myers Squibb, Pfizer, and Innogenetics; he serves on a scientific advisory board for En Vivo, Satori, and C2N Diagnostics; and receives grants to his institution from Pfizer, Eli Lilly, and Astra Zeneca. William Jagust serves as a consultant to Genentech, Bayer Healthcare, GE Healthcare. Synarc, Otsuka Pharmaceuticals, Janssen Alzheimer Immunotherapy, Merck, and Tau Rx. Ronald Petersen serves as a consultant for Elan Pharmaceuticals and GE Healthcare and serves on data monitoring committees for Pfizer, Inc., Janssen Alzheimer Immunotherapy. Peter Snyder serves as a consultant to CogState Ltd. Maria Carrillo is an employee of the Alzheimer's Association and reports no conflicts. Bill Thies is an employee of the Alzheimer's Association and reports no conflicts. Creighton Phelps is an employee of the U.S. Government and reports no conflicts.

[o]Alzheimer's Association, Chicago, IL, USA

[p]National Institute on Aging, Bethesda, MD, USA

Abstract

The National Institute on Aging and the Alzheimer's Association charged a workgroup with the task of developing criteria for the symptomatic predementia phase of Alzheimer's disease (AD), referred to in this article as mild cognitive impairment due to AD. The workgroup developed the following two sets of criteria: (1) core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis, and (2) research criteria that could be used in clinical research settings, including clinical trials. The second set of criteria incorporate the use of biomarkers based on imaging and cerebrospinal fluid measures. The final set of criteria for mild cognitive impairment due to AD has four levels of certainty, depending on the presence and nature of the biomarker findings. Considerable work is needed to validate the criteria that use biomarkers and to standardize biomarker analysis for use in community settings.

Keywords

Mild cognitive impairment; AD dementia; Diagnosis

1. Introduction

The National Institute on Aging and the Alzheimer's Association convened a working group to revise the diagnostic criteria for the symptomatic predementia phase of Alzheimer's disease (AD). Details of the selection and the charge to the working group are outlined in the Introduction to the revised criteria for AD that accompanies this article [1]. The present article summarizes the recommendations of the working group.

The working group was assembled because of growing consensus in the field that there is a phase of AD when individuals experience a gradually progressive cognitive decline that results from the accumulation of AD pathology in the brain. When the cognitive impairment is sufficiently great, such that there is interference with daily function, the patient is diagnosed with AD dementia. The dementia phase of AD is the topic of a separate working group report [2]. It is important to note that, as AD is a slow, progressive disorder, with no fixed events that define its onset, it is particularly challenging for clinicians to identify transition points for individual patients. Thus, the point at which an individual transitions from the asymptomatic phase to the symptomatic predementia phase [3], or from the symptomatic predementia phase to dementia onset, is difficult to identify [2]. Moreover, there is greater diagnostic uncertainty earlier in the disease process. It is, nevertheless, important to incorporate this continuum of impairment into clinical and research practice.

Two general principles underlie the recommendations presented in this report: (1) The *Core Clinical Criteria* outlined later in the text are designed to be used in all clinical settings. The working group believes that it is essential to have clinical criteria that can be applied broadly, in any setting, without the need of highly specialized tests and/or procedures. (2) The *Clinical Research Criteria* outlined later in the text, which incorporate the use of biomarkers, are currently intended to be used only in research settings, including academic centers and clinical trials. There are several reasons for this limitation: (1) more research needs to be done to ensure that the criteria that include the use of biomarkers have been appropriately designed, (2) there is limited standardization of biomarkers from one locale to

another, and limited experience with cut-points for diagnosis, and (3) access to biomarkers may be limited in different settings.

As a result, some aspects of the clinical research criteria may need to be revised, as these criteria are put into practice and new findings emerge. The clinical research criteria include an outline of additional data that need to be acquired so as to refine and improve their application. From that perspective, the clinical research criteria are designed to be a work-in-progress that will be updated regularly, as new information becomes available.

In these recommendations, we use the term "mild cognitive impairment (MCI) due to AD" to refer to the symptomatic predementia phase of AD. This degree of cognitive impairment is not normal for age and, thus, constructs such as age-associated memory impairment and age-associated cognitive decline do not apply. From this perspective, MCI due to AD can be considered as a subset of the many causes of cognitive impairment that are not dementia (CIND), including impairments resulting from head trauma, substance abuse, or metabolic disturbance [4].

Thus, the concept of *"MCI due to AD"* is used throughout this article to reflect the fact that the ultimate focus of these criteria is to identify those symptomatic but nondemented individuals whose primary underlying pathophysiology is AD. Similar to AD dementia, MCI due to AD cannot be currently diagnosed by a laboratory test, but requires the judgment of a clinician. Thus, MCI is a syndrome defined by clinical, cognitive, and functional criteria [5,6]. Also, similar to AD dementia, etiologies in addition to AD pathophysiological processes may coexist in an individual who meets the criteria for MCI due to AD. Nevertheless, similar to the criteria proposed by the International Working Group of Dubois et al [7], these criteria assume that it is possible to identify those individuals with AD pathophysiological processes as the likely *primary* cause of their progressive cognitive dysfunction [8–10].

2. Core clinical criteria for the diagnosis of MCI

In this section, we outline the core clinical criteria for individuals with MCI. In considering the specifics of this clinical and cognitive syndrome, it is important to emphasize, as noted earlier in the text, that sharp demarcations between normal cognition and MCI and between MCI and dementia are difficult, and clinical judgment must be used to make these distinctions.

2.1. MCI—Criteria for the clinical and cognitive syndrome

2.1.1. Concern regarding a change in cognition—There should be evidence of concern about a change in cognition, in comparison with the person's previous level. This concern can be obtained from the patient, from an informant who knows the patient well, or from a skilled clinician observing the patient.

2.1.2. Impairment in one or more cognitive domains—There should be evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background. If repeated assessments are available, then a decline in performance should be evident over time. This change can occur in a variety of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. An impairment in episodic memory (i.e., the ability to learn and retain new information) is seen most commonly in MCI patients who subsequently progress to a diagnosis of AD dementia. (See the section on the cognitive characteristics later in the text for further details).

2.1.3. Preservation of independence in functional abilities—Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance. It is recognized that the application of this criterion is challenging, as it requires knowledge about an individual's level of function at the current phase of their life. However, it is noteworthy that this type of information is also necessary for the determination of whether a person is demented.

2.1.4. Not demented—These cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning. It should be emphasized that the diagnosis of MCI requires evidence of intraindividual change. If an individual has only been evaluated once, change will need to be inferred from the history and/or evidence that cognitive performance is impaired beyond what would have been expected for that individual. Serial evaluations are of course optimal, but may not be feasible in a particular circumstance.

2.2. Cognitive characteristics of MCI

It is important to determine whether there is objective evidence of cognitive decline, and if so, the degree of this decline in the reports by the individual and/or an informant. Cognitive testing is optimal for objectively assessing the degree of cognitive impairment for an individual. Scores on cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers on culturally appropriate normative data (i.e., for the impaired domain(s), when available). It is emphasized that these ranges are guidelines and not cutoff scores.

2.2.1. Cognitive assessment—As noted earlier in the text, impairment in episodic memory (i.e., the ability to learn and retain new information) is most commonly seen in MCI patients who subsequently progress to a diagnosis of AD dementia. Research studies have shown that there are a variety of episodic memory tests that are useful for identifying those MCI patients who have a high likelihood of progressing to AD dementia within a few years. These tests share the characteristic that they assess both immediate and delayed recall, so that it is possible to determine retention over a delay. Many, although not all, of the tests that have proven useful in this regard are word-list learning tests with multiple trials. Such tests reveal the rate of learning over time, as well as the maximum amount acquired over the course of the learning trials. They are also useful for demonstrating that the individual is, in fact, paying attention to the task on immediate recall, which then can be used as a baseline to assess the relative amount of material retained on delayed recall. Examples of such tests include (but are not limited to): the Free and Cued Selective Reminding Test, the Rey Auditory Verbal Learning Test, and the California Verbal Learning Test. Other episodic memory measures include: immediate and delayed recall of a paragraph such as the Logical Memory I and II of the Wechsler Memory Scale Revised (or other versions) and immediate and delayed recall of nonverbal materials, such as the Visual Reproduction subtests of the Wechsler Memory Scale-Revised I and II.

Because other cognitive domains can be impaired among individuals with MCI, it is important to examine domains in addition to memory. These include: executive functions (e.g., set-shifting, reasoning, problem-solving, planning), language (e.g., naming, fluency, expressive speech, and comprehension), visuospatial skills, and attentional control (e.g., simple and divided attention). Many validated clinical neuropsychological measures are available to assess these cognitive domains, including (but not limited to): the Trail Making

Test (executive function), the Boston Naming Test, letter and category fluency (language), figure copying (spatial skills), and digit span forward (attention).

If formal cognitive testing is not feasible, then cognitive function can be assessed using a variety of simple, informal techniques. For example, the clinician can ask a patient to learn a street address and to recall it after a delay interval of a few minutes (e.g., John Brown, 42 Market Street, Chicago). Alternatively, the clinician can ask the patient to name three objects (e.g., a pen, a paper clip, and a dollar bill), place them in different locations around the room and subsequently ask the patient to recall the names of the objects and their locations, again after a brief delay. These types of approaches are relatively easy to perform during an office visit, and will yield informative results. It is important, however, for clinicians to recognize that these informal tests will likely be insensitive to subtle cognitive dysfunction during the early stages of MCI, and will often yield normal performance. In addition, these approaches typically do not assess cognitive domains beyond memory.

Finally, it must be recognized that atypical clinical presentations of AD may arise, such as the visual variant of AD (involving posterior cortical atrophy) or the language variant (sometimes called logopenic aphasia), and these clinical profiles are also consistent with MCI due to AD.

2.2.2. Summary of clinical and cognitive evaluation—The initiation of a clinical and cognitive evaluation typically includes a cognitive concern expressed by the patient, an informant, or a clinician observing the patient's performance. Cognitive decline can be documented by means of the history from the patient, preferably corroborated by an informant, or on the basis of observation by the clinician. Ideally, if serial assessments are available, they would be preferable, but in the setting of a single evaluation, this information is inferred from the history. The patient's cognition is assessed and found to be outside the normal range of function for the patient's age and educational background, but not sufficiently impaired to constitute dementia. The impairment can involve one or more cognitive domains. The clinician determines whether memory is prominently impaired, or whether the impairments in other cognitive domains predominate, such as spatial or language impairment. Typically, memory is the most common domain involved among patients who subsequently progress to AD dementia, as noted earlier in the text. There is generally mild functional impairment for complex tasks, but basic activities of daily living should be preserved, and the person should not meet criteria for dementia. It should be noted that the clinical syndrome, as summarized in this section and Table 1, is almost identical to the one previously described by Petersen et al [5,6,11].

2.2.3. Longitudinal cognitive evaluation—Evidence of progressive decline in cognition provides additional evidence that the individual has "MCI due to AD," as noted earlier in the text. Thus, it is important to obtain longitudinal assessments of cognition, whenever possible. It is recognized that a diagnosis will likely need to be given without the benefit of this information; however, obtaining objective evidence of progressive declines in cognition over time is important for establishing the accuracy of the diagnosis, as well as for assessing any potential treatment response.

2.2.4. Cautionary issues pertaining to cognitive assessment—It is important to emphasize that virtually all cognitive tests are sensitive to differences in age, education (i.e., literacy), and/or cultural variation among individuals. Age and educational norms are available for some tests, but few have norms that pertain to the oldest old (individuals aged ≥90 years). Moreover, considerable work remains to establish the reliability of cognitive tests across populations with wide cultural variation.

2.3. Etiology of the MCI clinical and cognitive syndrome consistent with AD

Once it has been determined that the clinical and cognitive syndrome of the individual is consistent with that associated with AD, but that the individual is not demented, the clinician must determine the likely primary cause, for example, degenerative, vascular, depressive, traumatic, medical comorbidities, or mixed disease. Typically, this information is derived from further historical information and ancillary testing (e.g., neuroimaging, laboratory studies, and neuropsychological assessment) that may prove informative.

To meet the core clinical criteria for MCI, it is necessary to rule out other systemic or brain diseases that could account for the decline in cognition (e.g., vascular, traumatic, medical). The goal of such an evaluation is to increase the likelihood that the underlying disease is a neurodegenerative disorder with characteristics consistent with AD. This diagnostic strategy is similar to the one that is used to diagnose "dementia due to AD." This may include seeking evidence for: (1) Parkinsonism, including prominent visual hallucinations, and rapid eye movement sleep abnormalities, often seen in dementia with Lewy bodies, (2) multiple vascular risk factors and/or the presence of extensive cerebrovascular disease on structural brain images, which is suggestive of vascular cognitive impairment, (3) prominent behavioral or language disorders early in the course of disease that may reflect frontotemporal lobar degeneration, or (4) very rapid cognitive decline that occurs over weeks or months, typically indicative of prion disease, neoplasm, or metabolic disorders. It should be noted that the pathological features of some of these disorders can exist in combination with AD (e.g., Lewy bodies and vascular disease), particularly among individuals at an advanced age.

The presence of vascular pathology, in the setting of MCI, is particularly challenging from a diagnostic perspective. Because AD pathology frequently coexists with vascular pathology, particularly at older ages, both may contribute to cognitive dysfunction. Thus, during life, it may be difficult to determine which pathological feature is the primary cause of the cognitive impairment.

Among the oldest old (i.e., those aged ≥90 years), there are additional difficulties in determining the etiology of the cognitive decline. For example, the pathological criteria for AD remain unclear for the oldest old.

2.3.1. Role of autosomal genetic mutations for AD—An additional issue is the role of genetics in the diagnosis. If an autosomal dominant form of AD is known to be present (i.e., mutation in *APP, PS1, PS2*), then the development of MCI is most likely the prodrome to AD dementia. The large majority of these cases develop early onset AD (i.e., onset below 65 years of age). There remains, however, variable certainty about the time course over which the progression from MCI to AD dementia will evolve in these individuals [12].

2.3.2. Role of genes that increase risk for AD—In addition, there are genetic influences on the development of late onset AD dementia. To date, the presence of one or two ε 4 alleles in the apolipoprotein E (*APOE*) gene is the only genetic variant broadly accepted as increasing risk for late-onset AD dementia, whereas the ε2 allele decreases risk. Evidence suggests that an individual who meets the clinical, cognitive, and etiologic criteria for MCI, and is also *APOE* ε4 positive, is more likely to progress to AD dementia within a few years than an individual without this genetic characteristic. It has been hypothesized that many additional genes play an important, but smaller role than *APOE*; these additional genes will also confer changes in risk for progression to AD dementia [13].

3. MCI—Research criteria incorporating biomarkers

In this section, we discuss the use of biomarkers in the diagnosis of "MCI due to AD." Much has been learned about the application of biomarkers to individuals with MCI. Thus, it seems important to incorporate this knowledge into the diagnostic framework outlined in these recommendations, recognizing as noted earlier in the text, that as new information emerges, it may be necessary to revise the way in which these recommendations incorporate biomarkers.

Two fundamental issues about individuals with MCI may be answered by the use of biomarkers: (1) To establish support for the underlying etiology of the clinical syndrome in an individual with MCI, which will have major importance for choosing the correct therapy, when effective treatments are available. (2) To determine the likelihood of cognitive and functional progression for an individual MCI patient to a more severe stage of MCI or to dementia, and the likelihood that this progression will occur within a defined period.

These questions are clearly interdependent, as different underlying etiologies can confer different prognoses for progression. However, a biomarker that is useful for defining an etiology may or may not be useful for prognostication, and vice versa. The different properties of biomarkers will ultimately drive their use in clinical situations, such as deciding whom to treat, as well as research situations that might include selection of subjects for clinical trials or for inclusion in longitudinal research studies. In addition, because the timing of progression to dementia is important, different biomarkers may have differential utility over the short- and long-term.

Biomarkers may be divided into several different classes. Some biomarkers directly reflect the pathology of AD by providing evidence of the presence of key proteins deposited in the brain during the course of AD, such as the beta-amyloid protein (Aβ) and tau [14]. Other biomarkers provide less direct or nonspecific evidence of AD by tracking a variety of indices of neuronal injury. These biomarkers may also have some specificity for AD, by virtue of the regional pattern of abnormalities. Conversely, other biomarker patterns can be useful in providing evidence of an alternative non-AD underlying cause.

The current pathological criteria for AD require evidence of Aβ deposition in plaques, along with evidence of tau deposition in neurofibrillary tangles. Evidence suggests that together the buildup of these two proteins in the brain is associated with neuronal injury. Thus, for the clinical research criteria proposed in this report to be based on the established pathological criteria, we have defined biomarkers in terms of whether they reflect Aβ deposition, tau deposition, or signs of neuronal injury.

Markers of Aβ deposition include both cerebrospinal fluid (CSF) measures of lower $A\beta_{42}$ levels [14–16] and positron-emission tomography (PET) evidence of Aβ deposition, using a variety of specific ligands [17]. Markers of tau accumulation include CSF measures of increased total tau or phosphorylated-tau (p-tau) [14–16].

It should be noted that increased Aβ deposition is seen in disorders other than AD (e.g., amyloid angiopathy). Likewise, although elevated levels of tau are clearly associated with AD, this finding may also occur in other neurodegenerative disorders (e.g., prion diseases). However, evidence of damage to neurons and synapses may also derive from direct measurement of tau (both total tau and p-tau) in the CSF, thus alterations in tau appear to be more nonspecific than the alterations in Aβ. Therefore, in these recommendations, CSF tau is considered to be a strong marker of the neuronal injury associated with AD. However, the two biomarkers in combination are extremely informative. Together with low CSF $A\beta_{42}$, elevated CSF tau provides a high likelihood of progression to AD in patients with MCI.

Measures of downstream neuronal injury include a number of structural and functional measures, including brain atrophy, and hypometabolism or hypoperfusion obtained with magnetic resonance imaging (MRI), PET, and single-photon emission computed tomography (SPECT) imaging [18–20].

A third group of biomarkers reflect biochemical changes related to processes such as cell death, synaptic damage, oxidative stress, or inflammation that may be part of the cascade of events that mediate damage, or the response to damage, in AD.

The major biomarkers in each of these categories are discussed later in the text and listed in Table 2.

3.1. Biomarkers reflecting Aβ

The amyloid plaques that are a hallmark feature of a pathological diagnosis of AD are reflected in biomarkers that can detect and quantify the Aβ protein that accumulates in the brain, as noted earlier in the text. This protein can be measured directly in CSF and plasma, however, the levels in CSF directly reflect the presence/amount of cerebral Aβ deposits (e.g., lower $A\beta_{42}$). PET scanning with a variety of ligands, some of which are still under development, can also detect fibrillar Aβ. CSF $A\beta_{42}$ and PET measures of fibrillar Aβ are strongly and inversely correlated with one another, and appear to reflect Aβ deposition in the brain [17].

Current evidence suggests that markers of amyloid pathology (i.e., CSF and PET) precede evidence of neuronal injury. This does not prove that Aβ is the initiating factor for the disease. However, it does suggest that these different categories of biomarkers seem to provide different sorts of information about the progress of disease in the brain.

3.2. Biomarkers reflecting neuronal injury

Elevated levels of tau are clearly associated with AD pathophysiological processes, as noted earlier in the text. However, changes in tau and phosphorylated-tau can also reflect general damage to neurons and synapses. In addition, AD also results in a wide range of structural and functional changes in the brain that have diagnostic and prognostic value in dementia and MCI, which appear to reflect damage to neurons and synapses. Many of these changes have topographic specificity for the neural damage or dysfunction that occurs in AD. Particular patterns of sequential involvement are characteristic of AD as well. Examples include loss of hippocampal volume seen on MRI, and reduction of glucose metabolism or perfusion in temporoparietal cortex that may be detected with PET or SPECT scanning. Although these biomarkers have been associated with the neuropathology of AD, regional atrophy, global atrophy, and regional hypometabolism and hypoperfusion are not specific for AD. These measures appear to provide evidence about the stage or severity of disease that may not be provided by Aβ biomarkers [21].

Other approaches to detection of downstream neuronal injury include the use of structural and functional measures that reflect more complex patterns of tissue loss or metabolic loss obtained with imaging procedures. These measures may be derived from data-driven statistical approaches in which many different brain regions are evaluated simultaneously. In these cases, replication and generalizability of findings must be demonstrated to develop data that can be used at the level of individual subject prediction.

Other techniques for which less data are currently available include diffusion tensor imaging, magnetic resonance spectroscopy, functional MRI, and resting BOLD functional connectivity. MRI perfusion has shown results similar to both SPECT/PET perfusion and PET metabolism, but available data are more limited.

3.3. Associated biochemical change

AD is characterized by numerous biochemical events, including oxidative stress (e.g., isoprostanes) and inflammation (e.g., cytokines). CSF, plasma, and imaging markers of these processes may provide information about specific pathways that are abnormal and could also provide information suggestive of underlying pathology. Additional work in this area is needed to know how useful these markers will be.

3.4. Limitations of current state of knowledge regarding biomarkers for AD

Many studies have used biomarkers to predict cognitive decline or progression to dementia among MCI patients, and most of the biomarkers in Table 2 are reported to be valuable in this situation. By contrast, there are several important limitations to current knowledge [22].

Few biomarkers have been compared with one another in multivariate studies, few have been validated with postmortem studies, and the use of combinations of biomarkers in studies has been limited. Therefore, it is currently difficult to understand the relative importance of different biomarkers when used together, and to interpret results when biomarker data conflict with one another.

Equally important, there is a dearth of truly predictive studies at the individual subject level or in unselected populations. Many biomarker studies report differences between “converters” and “stable” groups of subjects analyzed retrospectively (i.e., with subsequent knowledge of which subjects progressed to dementia).

Few studies define a specific cutoff value for a biomarker or biomarkers and then prospectively test its predictive accuracy. Effective use of biomarkers in the clinical arena will require the ability to assign a likelihood of decline or progression to dementia in an individual person over a specific time interval through the use of a single or multiple biomarkers.

Another major limitation is knowledge about the timing of decline or progression to dementia because the ability to detect change is dependent on the period of observation or prediction. Some biomarkers seem to have utility in predicting change over relatively short periods of observation, such as over 1 to 3 years. It seems likely that other types of biomarkers would be useful in predicting change over longer periods, such as many years or even decades. A complete understanding of the role of biomarkers in prediction of decline in MCI will require both short and long-term periods of observation.

Finally, little is known about outcome when biomarkers provide conflicting results, as noted earlier in the text. When a panel of biomarkers is used, it is possible that for some individuals, one biomarker will be positive, one negative, and one equivocal. This is complicated further by the fact that the biomarkers examined to date are not always clearly positive or clearly negative, but vary in degree. The long-term significance of such findings may also vary with the length of follow-up.

From a clinical perspective, it is important to emphasize, as noted earlier in the text, that although substantial deposits of Aβ and tau are required for a pathological diagnosis of AD, changes in these molecular markers in CSF are seen in other disorders (e.g., amyloid angiopathy, dementia with Lewy bodies, prion disease). Thus, the application of biomarkers as part of the clinical evaluation should consider other potential disorders, based on the overall clinical presentation of the patient.

3.5. Application of biomarkers to the clinical research diagnosis of MCI due to AD

In this section, we discuss the way in which biomarkers increase the likelihood that the MCI syndrome is due to the pathophysiological processes of AD. This diagnostic scheme is based on the wealth of biomarker and clinicopathological studies available. These data suggest that the conjoint application of clinical criteria and biomarkers can result in various levels of certainty that the MCI syndrome is due to AD pathophysiological processes.

For the purposes of the diagnostic approach we propose in these recommendations, two categories of biomarkers have been the most studied and applied to clinical outcomes. In this article, they are referred to as "Aβ" (which includes CSF $A\beta_{42}$ or PET amyloid imaging) and "biomarkers of neuronal injury" (which refers to CSF tau/p-tau, hippocampal, or medial temporal lobe atrophy on MRI, and temporoparietal/precuneus hypometabolism or hypoperfusion on PET or SPECT).

The criteria outlined later in the text are aimed at defining the level of certainty that the AD pathophysiological process is the underlying cause of the MCI syndrome in a given patient. The hypothesis underlying this classification scheme is that the evidence of both Aβ, and neuronal injury (either an increase in tau/p-tau or imaging biomarkers in a topographical pattern characteristic of AD), together confers the highest probability that the AD pathophysiological process is present. Conversely, if these biomarkers are negative, this may provide information concerning the likelihood of an alternate diagnosis. It is recognized that biomarker findings may be contradictory and that much remains to be learned about the outcome in these situations.

Currently, CSF $A\beta_{42}$ and tau measures, the ratio of CSF tau/$A\beta_{42}$, PET amyloid measures, and other biomarkers of neuronal injury such as hippocampal atrophy and temporoparietal hypometabolism have all been shown to predict progression of MCI to dementia. Whether one of these measures or a combination of them is more sensitive than the other, and whether quantitative values provide more information than a dichotomous rating are yet to be determined conclusively. It is also not yet known whether the best predictions of the actual rate of progression depend on the degree to which an individual expresses biomarkers of neuronal injury.

It is important to emphasize that standardization of these biomarkers is currently limited, and results often vary from laboratory to laboratory. Ultimately, it will be necessary to interpret biomarker data in the context of well-established normative values. "Positive" or abnormal values should fall within reliable and valid pathological ranges. Moreover, procedures for acquisition and analysis of samples need to be established to implement these biomarker criteria on a broad scale. Finally, although we consider biomarkers as "negative" or "positive" for purposes of classification, it is recognized that varying severities of an abnormality may confer different likelihoods or prognoses, which is currently difficult to quantify accurately for broad application.

In the coming years, when many of the unknown issues have been resolved, biomarkers reflecting AD pathophysiological processes in an individual with MCI will have two implications, depending on whether their levels fall within a range that supports the diagnosis of "MCI due to AD." First, if therapies directed at one or both of these two pathological proteins are being tested, or are effective for AD, then their detection with these biomarkers should indicate appropriate patient selection in terms of those most likely to derive therapeutic benefit. Second, detection of these biomarkers will predict a higher rate of cognitive and functional progression in patients with MCI whose biomarkers are positive as compared with MCI patients whose biomarkers are negative.

3.6. Biomarkers and levels of certainty for the diagnosis of MCI due to AD

In this section, we outline a probabilistic framework for the way in which biomarkers may be used to provide increasing levels of certainty that AD pathology is the cause of an individual's cognitive decline. That is, for those MCI subjects whose clinical and cognitive MCI syndrome is consistent with AD as the etiology, the addition of biomarkers would affect levels of certainty in the diagnosis.

In the most typical example in which the clinical and cognitive syndrome of MCI has been established, including evidence of an episodic memory disorder and a presumed degenerative etiology, the most likely cause is the neurodegenerative process of AD. However, the eventual outcome still has variable degrees of certainty. The likelihood of progression to AD dementia will vary with the severity of the cognitive decline and the nature of the evidence suggesting that AD pathophysiology is the underlying cause. Using the probabilistic framework proposed in these recommendations, positive biomarkers reflecting neuronal injury would increase the likelihood that progression to dementia will occur within a few years; however, positive findings reflecting both Aβ accumulation and neuronal injury together would confer the highest likelihood that the diagnosis is MCI due to AD.

In the example of the MCI patient who presents with an executive, spatial, or language impairment, it is still possible for such an individual to progress to AD dementia, although with a lower frequency. Thus, these presentations of MCI need to be recognized. The role of biomarkers may be particularly useful in this setting. For example, if a patient presents with a prominent visuospatial deficit and has significant atrophy in the parieto-occipital region on MRI, one might suspect a degenerative etiology likely leading to posterior cortical atrophy or the visual variant form of AD. If positive evidence of Aβ accumulation were also obtained on the basis of amyloid imaging or CSF measures, then the diagnosis of "MCI due to AD" would have a high likelihood.

In the following sections, we describe this hypothetical framework by which biomarkers may be used to increase diagnostic accuracy. As emphasized earlier, **this hypothetical framework will need to be tested by future studies and revised, as future data are generated.**

3.6.1. Biomarkers indicating a high likelihood that the MCI syndrome is due to AD

a. *A positive Aβ biomarker and a positive biomarker of neuronal injury.* The evidence to date indicates that this confers the highest likelihood that AD pathophysiological processes are the cause of the cognitive dysfunction. In addition, individuals with this biomarker profile are more likely to decline or progress to dementia due to AD in relatively short periods.

3.6.2. Biomarkers indicating an intermediate likelihood that the MCI syndrome is due to AD

a A positive Aβ biomarker in a situation in which neuronal injury biomarkers have not been or cannot be tested.

Or

b A positive biomarker of neuronal injury in a situation in which Aβ biomarkers have not been or cannot be tested.

Individuals falling within either of these categories show a major aspect of the AD pathological process, but without full evidence of both Aβ deposition and the downstream neuronal damage that characterize AD. Such individuals are considered to have a somewhat lower likelihood of underlying AD than individuals in whom both categories of biomarkers are positive. Note that this category does not include individuals in whom the two types of biomarkers provide conflicting information. This category accounts for situations in which one group of biomarkers cannot be tested because of access to technology, cost, or other reasons.

3.6.3. Situations in which biomarker information is uninformative

a. Results fall within ambiguous ranges (neither clearly positive nor negative) or biomarkers conflict with one another. In this category are also individuals in whom biomarkers have NOT been obtained.

There are many situations in which our current understanding of biomarkers limits the utility of biomarker testing. Clearly, there are many situations in which no biomarker testing can be or will be performed. This is likely to be the case in many routine clinical applications of the MCI criteria. Furthermore, there are many potential situations in which biomarkers could offer conflicting results (i.e., a positive Aβ biomarker and a negative biomarker of neuronal injury or the reverse). There is little available evidence to interpret the importance of the many different possible combinations of such biomarker outcomes; thus, these situations are classified together as uninformative. Finally, we recognize that results do not always fall into clearly "positive" and "negative" ranges but may be ambiguous, and the importance of such findings is unknown.

3.6.4. Biomarkers that suggest that the MCI syndrome is unlikely to be due to AD

a. *Negative biomarkers for both Aβ and neuronal injury.* The definitive absence of evidence of either Aβ deposition or neuronal injury strongly suggests that the MCI syndrome is not due to AD. In such situations, search for biomarkers that reflect alternative pathological processes should be considered. Such biomarkers are not as well established as those for AD. They may include: (1) prominent frontal or frontotemporal hypometabolism, hypoperfusion, or atrophy that often reflects frontotemporal lobar degeneration, (2) loss of dopamine transporters seen with SPECT imaging, often seen in dementia with Lewy bodies, (3) a periodic electroencephalogram, diffusion-weighted imaging changes on MRI, or an extremely high CSF tau protein in someone with very rapid dementia progression (progression from normal to moderate or severe dementia in ≤6 months) is typically indicative of prion disease, or (4) the presence of extensive cerebrovascular disease on structural brain images, without any biomarkers characteristic of AD, which is suggestive that the syndrome reflects vascular cognitive impairment. In all of these cases, the risk of subsequent decline is related to the most likely underlying pathology and the potential treatments that may be available.

4. Proposed terminology for classifying individuals with "MCI due to AD" with varying levels of certainty

We propose the terminology for "MCI due to AD" in the following sections, incorporating the use of biomarkers. It is fully recognized that there are limitations in our knowledge about these biomarkers, as noted earlier. These criteria are designed to stimulate the application of biomarkers in clinical research settings, thus permitting refinements in these criteria over time (Table 3).

4.1. MCI—Core clinical criteria

Individuals in this category meet the Core Clinical Criteria for MCI, based on the characteristics of the clinical syndrome and an examination of potential etiologic causes for the cognitive decline, as outlined earlier in the text. This evaluation process is designed to increase the likelihood that the underlying disease responsible for the cognitive dysfunction is a neurodegenerative disorder with characteristics consistent with AD. However, if biomarkers have been obtained, but the aggregate information is considered uninformative, this diagnosis will also apply. This would occur in situations in which biomarker results conflict with one another, or in situations in which results fall in an indeterminate range that is neither clearly negative nor positive. Patients in this category have the typical presentation of individuals who are at an increased risk of progressing to AD dementia. As noted earlier in the text, these individuals typically have a prominent impairment in episodic memory, but other patterns of cognitive impairment can also progress to AD dementia over time (e.g., visuospatial impairments). Note that this category also applies to situations in which biomarkers have NOT been tested. This category is still consistent with the possibility that the patient with MCI has underlying AD pathology

4.2. MCI due to AD—Intermediate likelihood

If the subject meets the Core Clinical Criteria for MCI, but in addition has either a positive biomarker reflecting Aβ deposition with an untested biomarker of neuronal injury, or a positive biomarker reflecting neuronal injury with an untested biomarker of Aβ, then there is increased likelihood that the outcome will be AD dementia. Thus, in the absence of one of these categories of biomarker information, the situation is still consistent with an *intermediate level of certainty* that the individual will progress to AD dementia over time. Therefore, patients who meet the criteria for this diagnosis have an intermediate level of certainty that they have "MCI due to AD."

4.3. MCI due to AD—High likelihood

If the subject meets the Core Clinical Criteria for MCI, and in addition has positive biomarkers for both Aβ and neuronal injury, this provides *the highest level of certainty* that over time the individual will progress to AD dementia. Thus, patients who meet the criteria for this diagnosis have the highest level of certainty that they have "MCI due to AD," and that they will progress to AD dementia over time.

4.4. MCI—Unlikely due to AD

Patients who have negative biomarkers for both Aβ and neuronal injury are considered to have the lowest likelihood of underlying AD pathophysiology. Although such individuals may still have AD, a search for an alternate cause of the MCI syndrome is warranted.

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Table 1

Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria
Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
Preservation of independence in functional abilities
Not demented
Examine etiology of MCI consistent with AD pathophysiological process
Rule out vascular, traumatic, medical causes of cognitive decline, where possible
Provide evidence of longitudinal decline in cognition, when feasible
Report history consistent with AD genetic factors, where relevant

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

Table 2

Biomarkers under examination for AD

Biomarkers of Aβ deposition
CSF $A\beta_{42}$
PET amyloid imaging
Biomarkers of neuronal injury
CSF tau/phosphorylated-tau
Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
Rate of brain atrophy
FDG-PET imaging
SPECT perfusion imaging
Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures
Associated biochemical change
Inflammatory biomarkers (cytokines)
Oxidative stress (isoprostanes)
Other markers of synaptic damage and neurodegeneration such as cell death

Abbreviations: Aβ, beta-amyloid protein; CSF, cerebrospinal fluid; PET, positron emission tomography; FDG, fluorodeoxyglucose; SPECT, single photon emission tomography; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; BOLD, blood oxygen level-dependent; MR, magnetic resonance.

Table 3

MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI-core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG. fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

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Test–retest reliability analysis of the Cambridge Neuropsychological Automated Tests for the assessment of dementia in older people living in retirement homes

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Test–retest reliability analysis of the Cambridge Neuropsychological Automated Tests for the assessment of dementia in older people living in retirement homes

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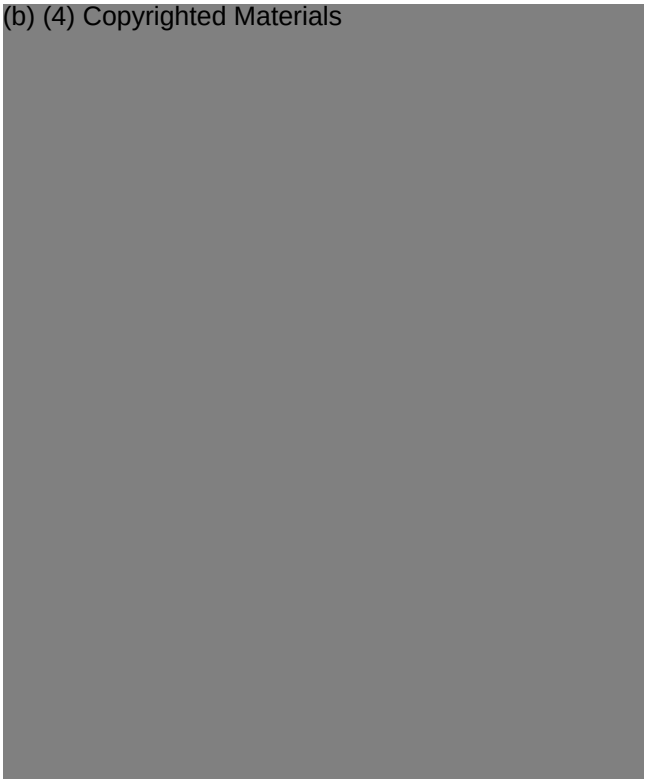
ABSTRACT

The validity of the Cambridge Neuropsychological Automated Tests has been widely studied, but their reliability has not. This study aimed to estimate the test–retest reliability of these tests in a sample of 34 older adults, aged 69 to 90 years old, without neuropsychiatric diagnoses and living in retirement homes in the district of Lisbon, Portugal. The battery was administered twice, with a 4-week interval between sessions. The Paired Associates Learning (PAL), Spatial Working Memory (SWM), Rapid Visual Information Processing, and Reaction Time tests revealed measures with high-to-adequate test–retest correlations (.71–.89), although several PAL and SWM measures showed susceptibility to practice effects. Two estimated standardized regression-based methods were found to be more efficient at correcting for practice effects than a method of fixed correction. We also found weak test–retest correlations (.56–.68) for several measures. These results suggest that some, but not all, measures are suitable for cognitive assessment and monitoring in this population.

KEYWORDS

Alzheimer disease; CANTAB; practice effects; reliable change index; standardized regression-based models

Introduction



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Pergamon

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Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues

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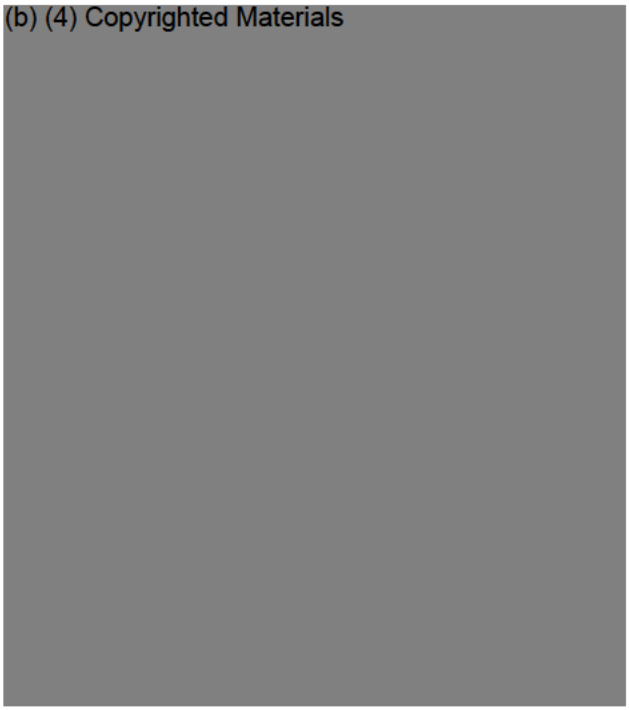
(*Received* 13 *October* 1997; *accepted* 26 *January* 1998)

Abstract—Neuropsychological test batteries are repeatedly administered to evaluate changes over time or the effects of clinical interventions. Relationships between scores on different tests within batteries are also examined to test models for associations between functional deficits. These comparisons may be misleading unless Test/Re-test reliability for individual tests is satisfactory. Interpretations of repeated measurements also depend on the extent to which improvement with practice varies between tasks and between more and less able individuals. Test/Re-test correlations and practice effects for two neuropsychological test batteries (CANTAB, ISPOCD) and from laboratory tasks commonly used in cognitive assessments of older people were obtained from large groups of healthy elderly. Tests in neuropsychological batteries varied markedly in test/re-test reliability which, in some cases, fell below levels considered methodologically acceptable. Putative measures of 'frontal' or 'executive' function, in which performance may be markedly improved by abrupt discovery of an appropriate strategy, were especially likely to show low reliability. Most tests showed significant practice effects, and on some these are substantial enough to compromise comparisons on repeated testing. On a minority of tests practice effects were counter-intuitive, in that less able showed significantly more gains than more able individuals.

Key Words: executive; strategy; change; frontal; memory; practice.

Introduction



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Characterization of cognitive function with the CANTAB in individuals with amnestic MCI in relation to hippocampal volume, amyloid and tau status: Preliminary baseline results from the PharmaCog/European-ADNI Study

Pradeep J Nathan[1,2], Rosemary Abbott[28], Samantha Galluzzi[3], Moira Marizzoni[4], Maria Cotelli[4], Cristina Bagnoli[4], Claudio Babiloni[5], David Bartres-Faz[6], Joëlle Micallef[7], Catherine Casse-Perrot[7], Laura Ianteaume[7], Regis Bordet[8], Beatriz Bosch[9], Francesca de Anna[10], Mira Didic[11], Lucia Farotti[12], Gianluigi Forloni[13], Jorge Jovicich[14], Camillo Marra[15], Nicola Marzano[5], Jose Luis Molinuevo[16], Flavio Nobili[17], Jeremie Pariente[18], Lucilla Parnetti[12], Pierre Payoux[19], Agnese Picco[17], Jean-Philippe Ranjeva[20], Luca Roccatagliata[21], Paolo Maria Rossini[15], Nicola Salvadori[12], Peter Schonknecht[22], Martin Berwig[22], Tilman Hensch[22], Andrea Soricelli[23], Magda Tsolaki[24], Fabrizio Vecchio[25], Pieter Jelle Visser[26], Jens Wiltfang[27], Daniele Orlandi[3], Andrew Blackwell[28], Olivier Blin[7], Giovanni Frisoni[29]

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Introduction

- Mild Cognitive Impairment (MCI) is a heterogeneous condition with differential underlying pathophysiologies.
- Accumulation of beta amyloid (Abeta) and/or Tau in the brain is associated with greater neurodegeneration and cognitive decline and a prelude to Alzheimer's disease (AD).
- Understanding MCI populations for hippocampal and fronto-striatal dependent memory deficits and biomarker abnormalities will help identify a more homogeneous population with a greater risk of developing AD.
- The objective of this study was to examine the relationship between performance on the CANTAB tasks probing hippocampal and fronto-striatal function, hippocampal volume and CSF biomarkers.

Methods

- Participants (aged 50-84) were recruited from the PharmaCog (E-ADNI; work package 5), European multicentre study (Table 1).
- Inclusion criteria: 1) subjective memory complaint, 2) 1SD deficit in memory (Logical memory II subscale – delayed paragraph recall), 3) MMSE between 24 and 30; 4) CDI=0.5 (Memory box at least 0.5); 5) diagnosis of amnestic MCI.
- 145 individuals underwent clinical and cognitive evaluation using the CANTAB tests, high resolution 3T MRI with MPRAGE and lumbar punctures for the assessment of cerebrospinal fluid (CSF) levels of Ab42, tau and p-tau. Individuals were divided into Amyloid+ (CSF-POS) and Amyloid- (CSF-NEG) based on CSF Ab42 levels (CSF-POS: >550 pg/ml); CSF-NEG: <550 pg/ml).
- The relationships between biomarkers and cognitive task performance were assessed through a series of linear regression models using LM in R software. All models were adjusted for age and years of education. Differences between CSF-POS and CSF-NEG group were assessed using t-tests or Chi squared tests.

Baseline Characteristics by CSF Amyloid Status	CSF Abeta (+ve) N=55		CSF Abeta (-ve) N=90		Overall N=145		Range	Significance
	Mean	SD	Mean	SD	Mean	SD		
Age (years)	69.8	6.7	68.8	7.7	68.2	7.3	50-84	T=-0.8 p=0.40
MMSE	26.0	1.8	27.0	1.8	26.6	1.9	23-30	T=3.1 p>=0.01
	Percent (%)		Percent (%)					
Gender (% male)	43.6	-	42.2	-	42.8	-		0.3 (df=1) p= .87
Education (% <=10y)	45.5	-	56.8	-	53.1	-		2.1 (df=1) p=.15

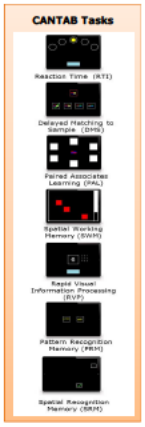
Table 1. Baseline characteristics by CSF Amyloid Status

Results

- At baseline, CSF-POS individuals showed worse performance relative to CSF-NEG individuals on fronto-striatal dependent recognition and working memory tasks (i.e. SRM, DMS and SWM) (Table 2), with effect sizes ranging from -0.12 to -0.66.
- Worse performance on the paired associate learning (PAL) task of episodic memory was associated with reduced hippocampal volume, higher CSF levels of tau and p-tau and increased Tau/Abeta42 ratio (Table 3). Worse performance on the pattern recognition memory (PRM) task (immediate and delayed) was also associated with reduced hippocampal volume. Both PAL and PRM were also associated with a functional outcome measure (i.e. FAQ)(Table 3). Worse performance on the spatial recognition memory (SRM) task was associated with low CSF levels of Abeta42, higher CSF levels of tau and p-tau and increased Tau/Abeta42 ratio (Table 3).
- Significant associations were also found between hippocampal volume, CSF biomarkers and spatial working memory (SWM), delayed matching to sample (DMS) and sustained attention (RVP) (Table 3).

	Overall		CSF Amyloid (+ve)		CSF Amyloid (-ve)	
	Mean	SD	Mean	SD	Mean	SD
RTI Five choice reaction time (median)	417.9	96.4	414.5	97.7	420.5	96.0
DMS % correct all delays	67.9	16.3	62.5***	16.6	72.0	14.9
PAL Total errors adjusted	70.5	40.1	73.3	38.3	68.5	41.6
SWM Between errors	42.4	21.3	47.4**	21.3	38.7	20.6
SWM Strategy	27.2	9.2	28.0	8.9	26.6	9.4
RVP A Prime	0.8	0.1	0.8	0.1	0.8	0.1
PRM immediate % correct	77.6	15.2	75.5	14.5	79.2	15.6
PRM delayed % correct	65.3	17.9	63.5	17.4	66.6	18.3
SRM % correct	63.7	13.5	58.7***	13.6	67.3	12.3
Neuropsychiatric Inventory Functional Assessment Questionnaire (FAQ)	8.8	10.3	9.6	11.1	8.3	9.7
Geriatric Depression Scale	2.5	2.3	2.6	2.5	2.5	2.3
	2.6	1.9	2.7	1.9	2.6	1.9
Abeta42 (pg/mL)	693.0	293.5	419.1***	86.9	860.4	245.1
p-tau (pg/mL)	67.6	34.8	79.1***	37.6	60.6	31.1
Tau (pg/mL)	475.5	346.4	556.4**	334.5	426.1	346.0
Left-Hippocampal Volume (mm^3)	3176.6	688.9	3131.8	682.2	3207.6	696.9
Right-Hippocampal Volume (mm^3)	3310.6	662.7	3176.1*	606.7	3403.6	687.8
IntraCranialVol (mm^3)	1338396.2	177864.9	1323908.3	186939.6	1348409.9	172006.4
Abeta (Positive) <550mL	37.9					
APOE e4 (%)						
APOE e4 allele (1 copy)	37.3		52.7***		27.8	
APOE e4 allele (2 copies)	8.3		20.0***		1.1	

Table 2. Cognition and Biomarker data; ***p<0.01 , **p<0.05 and *p<0.1 compared to CSF Amyloid (-ve)



	Memory Tasks						Executive Function	Sustained Attention	Processing Speed
	Episodic Memory	Working Memory	Recognition /Working Memory	Recognition Memory	Recognition Memory	Recognition Memory			
	PAL Errors	SWM Errors	DMS	SRM	PRM Immediate	PRM Delayed	SWM Strategy	RVP	RTI
Tau	***		**	*				***	
Ptau	**	*	*	**				***	
Abeta		***	***	**			**	*	
LHPV	***			*		**		**	
RHPV	***		*		**	*		***	
IC Vol							***		
CSF Abeta (+ve)		**	***	***					
Tau/Abeta	***	***	***	***				***	
GDS									
FAQ	***					***	**		
NPI		**					***		

Table 3. Relationship between cognitive function and biomarkers. *p <= 0.10, ** p<=0.05, *** p<0.01.
Paired Associates Learning (PAL) Total Errors Adjusted, Spatial Work ng Memory (SWM) Between Errors, Strategy Score, Delayed Matching to Sample (DMS), Spatial Recognition Memory (SRM), Pattern Recognition Memory (PRM), Immediate and Delayed (% correct), Rapid Visual Processing (RVP) A Prime, Reaction Time (RTI), Median 5 Choice Reaction Time, Functional Assessment Questionnaire (FAQ)Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI). Left Hippocampal Volume (LPHV), Right Hippocampal Volume (RHPV), Intracranial Volume (ICV)

Discussion

- CSF Amyloid+ individuals showed greater deficits in CANTAB tasks measuring fronto-striatal function compared to CSF Amyloid- individuals. These findings suggest that despite both groups having amnestic MCI with subjective and objective memory deficits at screening, Amyloid+ amnestic MCI individuals also show additional fronto-striatal deficits.
- CANTAB tasks measuring recognition and working memory and sustained attention were significantly associated with, 1) CSF Abeta42, tau, p-tau, Tau/Abeta42 and 2) hippocampal volume, with worse performance on these tasks associated with higher CSF tau, p-tau and tau/Abeta42 and lower Abeta42 and hippocampal volume (Figure 1).
- Hippocampal dependent tasks including PAL and PRM were associated with hippocampal volume. Performance on the PAL task of episodic memory was highly correlated with hippocampal volume (accounting for 26% of the variance) suggesting that it may a useful diagnostic marker for use alone or in combination with other biomarkers (i.e. hippocampal volume or CSF biomarkers) in identifying patients at risk of MCI.
- Hippocampal dependent memory (i.e. PAL and PRM) and fronto-striatal executive function (i.e. SWM strategy) were also associated with functional outcome.
- The findings have implications for identifying MCI patients at risk of developing AD and enriching a more homogenous population for clinical trials with fronto-striatal and hippocampal dependent attention and memory deficits, neurodegeneration and CSF biomarker abnormalities consistent with prodromal AD populations.

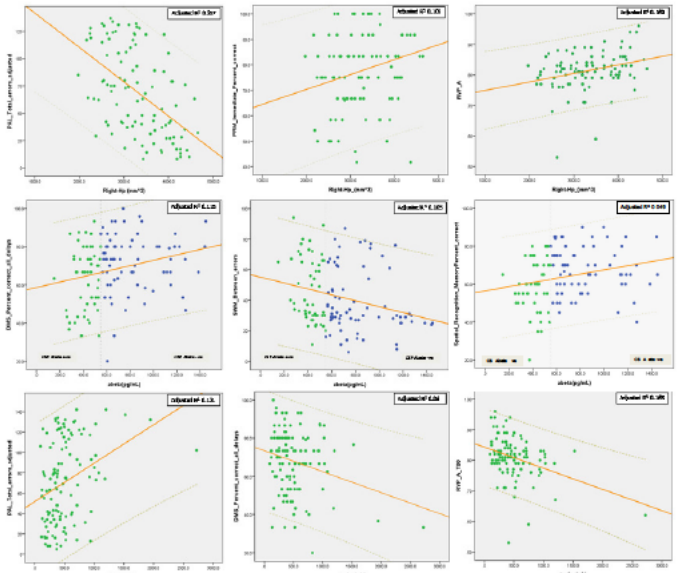


Figure 1. Relationship between cognitive function, CSF biomarkers and hippocampal volume.

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CANTAB Mobile

16. Software

Table of Documents

The following table summarizes documentation provided, based on the guidance in Table 3 of ***Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*** (May 11, 2005) for software designated Minor level of concern.

Table 1. Documentation Provided for Cantab Mobile, Designated Minor Level of Concern

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Name:	Andrew Blackwell	Role:	Commercial Representative
Signature:		Date:	

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Name:	Holger Reusch	Role:	Quality Manager
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PALD Development Review 001

Record ID: NMI-PALD-DEV-001 Release for approval: (b)(4)

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the record is approved for use.

Approval : Owner

(b)(4)

Approval : Additional

(b)(4)

Approval by the Quality Manager (QA), indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the record is approved for use.

QA Approval

(b)(4)

(b)

Title: PALD Validation Report

Docment ID: (b)(4)

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the document is approved for use.

Management Approval : Owner

(b)(4)

Management Approval : Additional

(b)(4)

Management Approval : Additional

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Management Approval : Additional

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Management Approval : Additional

(b)(4)

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CHANGE CONTROL (b)(4)
OWNER: IC

Date raised	Raised by	Project	Type	Priority
(b)(4)	IC	PALD (b)(4)	Planned	project-deadline

(b)(4)

(b)(4)

(b)(4)

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cambridge cognition

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the document is approved for use.

Management Approval : Owner

(b)(4)

Management Approval : Additional

(b)(4)

Management Approval : Additional

(b)(4)

Management Approval : Additional

(b)(4)

Management Approval : Additional

(b)(4)

Approval by the Quality Manager (QA), indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the document is approved for use.

Quality Assurance Approval

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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(b)(4)

PALD Design Review (b)(4)

Record ID: NMI-PALD-(b)(4) Release for approval: (b)(4)

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the record is approved for use.

Approval : Owner

(b)(4)

Management Approval

(b)(4)

Management Approval

(b)(4)

Approval by the Quality Manager (QA), indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the record is approved for use.

QA Approval

(b)(4)

(b)

(b)

(b)

PALD Development Review 002

Record ID: NMI-PALD(b)(4) Release for approval: 14/Mar/2012

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the record is approved for use.

Approval : Owner

(b)(4)

Approval : Additional

(b)(4)

Approval by the Quality Manager (QA), indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the record is approved for use.

QA Approval

(b)(4)

(b)

PALD Development Review (b)(4)

Record ID: NMI-PALD-(b)(4) Release for approval: (b)(4)

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the record is approved for use.

Approval : Owner

(b)(4)

Approval : Additional

(b)(4)

Approval by the Quality Manager (QA), indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the record is approved for use.

QA Approval

(b)(4)

(b)

(b)(4)

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the document is approved for use.

Management Approval : Owner

(b)(4)

Management Approval : Additional

Name:	Nick Taptiklis	Role:	Technical Lead
Signature:		Date:	

Management Approval : Additional

(b)(4)

Management Approval : Additional

(b)(4)

Management Approval : Additional

(b)(4)

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Date raised	Raised by	Project	Type	Priority
(b)(4)	IC	PALD (b) (4)	Emergency	target-date: (b)(4)

(b)(4)

Approval for change to proceed.

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the change is approved to proceed.

Name	Role	Date	Signature

(b)(4)

(b)

(b)

Title: PALD Validation Report

Docment ID: (b)(4)

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the document is approved for use.

Management Approval : Owner

(b)(4)

Management Approval : Additional

(b)(4)

Management Approval : Additional

(b)(4)

Management Approval : Additional

(b)(4)

Management Approval : Additional

(b)(4)

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CHANGE CONTROL (b)(4)

OWNER: IC

Date raised	Raised by	Project	Type	Priority
(b)(4)	IC	PALD (b)(4)	Emergency	target-date: (b)(4)

(b)(4)

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(b)

CHANGE CONTROL CR-NMI-008
OWNER: IC

Date raised	Raised by	Project	Type	Priority
(b)(4)	IC	PALD (b) (4)	Emergency	target-date: (b)(4)

(b)(4)

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Date raised	Raised by	Project	Type	Priority
(b)(4)	(	PALD (b)(4)	(b) (4)	(b) (4)

(b) (4) Copyrighted Materials

(b)

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(b) (4)

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PALD Development Review (b)

Record ID: (b)(4) Release for approval: (b)(4)

Approval by the following personnel signifies agreement that the content, rationale and approach are consistent with requirements, that a review for clarity, accuracy, completeness and compliance has been completed, and the record is approved for use.

Approval : Owner

(b)(4)

Approval : Additional

(b)(4)

Approval by the Quality Manager (QA), indicates that a review has been completed for clarity, accuracy, completeness and compliance with company standards and regulatory requirements and that the record is approved for use.

QA Approval

(b)(4)

(b)

PART 1 – CHANGE APPROVAL

Date raised	Raised by	Project	Type	Target resolution date
16/Jul/2015	NT	NMI	Emergency	TBC

(b)(4)

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(b)

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(b)

(b)

11. DEVICE DESCRIPTION

Product Name: Cantab Mobile (K161328))

Indication: Assess Memory by Testing Visuospatial Associative Learning in Patients Aged 50 to 90 Years

Sponsor

© Cambridge Cognition Limited
Tunbridge Court
Tunbridge Lane
Bottisham
Cambridge, CB25 9TU
UK
Tel: +44 (0) 1223 810 700
Fax: +44 (0) 1223 810 701

United States Agent

Clementi and Associates Ltd.
919 Conestoga Road
Rosemont, PA 19010

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(b)(4)

(b)(4)

(b)(4)

Sent: Thursday, August 11, 2016 12:36 PM
To: 'Binoy Mathews'
<binoy.mathews@fda.hhs.gov<mailto:binoy.mathews@fda.hhs.gov>>
Subject: RE: K161328 is on Hold Pending Your Response

Dear Mr. Matthews,

Cambridge Cognition has reviewed the detailed comments on the above referenced submission, provided in the "Deficiency List" dated July 15, 2016, and is preparing to submit the additional requested information. We do however request your clarification and guidance on one question, #6, which is restated below for your convenience. If the Sponsor's attached comments do not resolve the concern, we request a teleconference to discuss this aspect of the application further, in order to submit a complete response.

"6. (b)(4)
(b)(4)

a. (b)(4)
(b)(4)
. . . . . "

We look forward to your follow up response. If we need to submit this in an alternative format we are happy to do so, but will await your guidance.

Regards,

Nancy Clementi

Nancy Durst Clementi, M.D.
Clementi and Associates, Ltd
919 Conestoga Road
Building 3, Suite 312
Rosemont, PA 19010
610-527-2600

From: Binoy Mathews [mailto:binoy.mathews@fda.hhs.gov]
Sent: Friday, July 15, 2016 11:05 AM
To: Nancy Clementi
<Nancy.Clementi@clempharma.net<mailto:Nancy.Clementi@clempharma.net>>
Cc: Binoy Mathews
<binoy.mathews@fda.hhs.gov<mailto:binoy.mathews@fda.hhs.gov>>
Subject: K161328 is on Hold Pending Your Response

July 15, 2016

We have reviewed your submission K161328 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, referencing the submission number K161328 to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please refer to the eCopy guidance at
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf for current information on the number of copies and the format (paper versus eCopy) you must submit.

Your response is due within 180 days from the date of this request, which is January 11, 2017. If a complete response is not received in CDRH's Document Control Center within 180 days, we will consider this submission to be withdrawn, and we will delete it from our review system.

You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission to the Document

Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.

Should you have questions about this email, you may contact Binoy Mathews, the lead reviewer assigned to your submission.

*** This is a system-generated email notification ***

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Thursday, September 08, 2016 8:41 AM
To: Mathews, Binoy
Subject: RE: K161328 is on Hold Pending Your Response

Hi Binoy,

Thanks for your follow up on our query. I have spoken to the Sponsor this morning and we will move forward with your suggestions. Based upon the work already completed on the response submission I believe we will be submitting our official response in about 6 weeks' time (allowing for internal sign-offs at the Sponsor). I will let you know if there is going to be any significant change in that timeline.

Thanks again for your help!

Best,

Nancy

From: Mathews, Binoy [mailto:Binoy.Mathews@fda.hhs.gov]
Sent: Wednesday, September 07, 2016 3:42 PM
To: Nancy Clementi <Nancy.Clementi@clempharma.net>
Subject: RE: K161328 is on Hold Pending Your Response

Hi Nancy,
Hope you are well. The review team had a chance to meet and discuss your proposed response to question #6 from FDA's deficiency list dated July 15, 2016. (b)(4)
(b)(4)

(b)(4) I hope this information proves useful. Please do contact me if you have any further questions or concerns.

Regarding your new submission. The assignment of submissions is normally done based on reviewer workload. At times it may go to the same reviewer however this is not guaranteed. You may make this request within your cover letter.

Regarding K161328, it would be helpful if you could kindly let me know when you plan on submitting your official response to FDA.

Many thanks!

--Binoy

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Monday, August 29, 2016 11:36 AM
To: Mathews, Binoy
Subject: RE: K161328 is on Hold Pending Your Response

Dear Binoy,

Please don't apologize. It is summer and everyone is busy, covering for vacationing colleagues and hopefully getting in some vacation time as well! Later this week or after the holiday weekend is absolutely fine. We have been very pleased with the responsiveness and quality of the response from your team, and appreciate your help.

While I remember to ask . . . . .Once we resolve the questions on this application, Cambridge Cognition wants to submit another closely related application. Is there some way to ensure that the same review team is assigned? We think it would save work on the FDA side.

Best,

Nancy

From: Mathews, Binoy [mailto:Binoy.Mathews@fda.hhs.gov]
Sent: Monday, August 29, 2016 10:45 AM
To: Nancy Clementi <Nancy.Clementi@clempharma.net>
Subject: RE: K161328 is on Hold Pending Your Response

Hi Nancy,

Many thanks for your email. I apologize for the delay in getting back to you. I am scheduled to meet with the clinical reviewer this week regarding your response. I apologize for the time taken, but everyone has been very busy and hence the difficulty. Would it be alright if I could provide you with our feedback by Wednesday or Thursday of this week? I hope that would be acceptable. Kindly let me know. Many thanks!

Regards,

Binoy

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Monday, August 29, 2016 10:37 AM
To: Mathews, Binoy
Subject: FW: K161328 is on Hold Pending Your Response

Mr. Matthews,

Can you please advise if we should submit this request for clarification and guidance via some other mechanism? Many thanks in advance.

Nancy Clementi, M.D.
US Agent for Cambridge Cognition
610-627-2600

From: Nancy Clementi
Sent: Thursday, August 11, 2016 12:36 PM
To: 'Binoy Mathews' <binoy.mathews@fda.hhs.gov>
Subject: RE: K161328 is on Hold Pending Your Response

Dear Mr. Matthews,

(b)(4) [redacted] If the Sponsor's attached comments do not resolve the concern, we request a teleconference to discuss this aspect of the application further, in order to submit a complete response.

"6. (b)(4) [redacted]
(b)(4) [redacted]

a. (b)(4) [redacted]

We look forward to your follow up response. If we need to submit this in an alternative format we are happy to do so, but will await your guidance.

Regards,

Nancy Clementi

Nancy Durst Clementi, M.D.
Clementi and Associates, Ltd
919 Conestoga Road
Building 3, Suite 312
Rosemont, PA 19010
610-527-2600

From: Binoy Mathews [mailto:binoy.mathews@fda.hhs.gov]
Sent: Friday, July 15, 2016 11:05 AM
To: Nancy Clementi <Nancy.Clementi@clempharma.net>
Cc: Binoy Mathews <binoy.mathews@fda.hhs.gov>
Subject: K161328 is on Hold Pending Your Response

July 15, 2016

We have reviewed your submission K161328 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, referencing the submission number K161328 to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please refer to the eCopy guidance at
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf
for current information on the number of copies and the format (paper versus eCopy) you must submit.

Your response is due within 180 days from the date of this request, which is January 11, 2017. If a complete response is not received in CDRH's Document Control Center within 180 days, we will consider this submission to be withdrawn, and we will delete it from our review system.

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If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission to the Document Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.

Should you have questions about this email, you may contact Binoy Mathews, the lead reviewer assigned to your submission.

*** This is a system-generated email notification ***

FYI...

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Wednesday, January 11, 2017 11:49 AM
To: Mathews, Binoy
Subject: RE: K161328/S001

Good morning Binoy,

(b)(4)

Thank for your help.

Best,

Nancy

From: Mathews, Binoy [mailto:Binoy.Mathews@fda.hhs.gov]
Sent: Wednesday, January 11, 2017 11:24 AM
To: Nancy Clementi
<Nancy.Clementi@clempharma.net<mailto:Nancy.Clementi@clempharma.net>>
Subject: RE: K161328/S001

Hi Nancy,

Thanks for sending us the revisions. I just wanted to clarify one thing with you. Will the new language regarding mood scores be included on the electronic report made available to the clinician. Kindly let me know. Thanks!

Regards,

Binoy

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Monday, January 09, 2017 9:57 AM
To: Mathews, Binoy
Subject: RE: K161328/S001

Good morning Binoy,

I wanted to send a quick note to ask if you have what you need from Cambridge Cognition. . . . . we are prepared to make any additional changes you may wish, so just let me know.

Best,

Nancy

From: Mathews, Binoy [mailto:Binoy.Mathews@fda.hhs.gov]
Sent: Thursday, January 05, 2017 11:25 AM

To: Nancy Clementi
<Nancy.Clementi@clempharma.net<mailto:Nancy.Clementi@clempharma.net>>
Subject: K161328/S001

Hi Nancy,

Happy New Year! Your 510k Supplement is currently under review. We have a few concerns which we believe can be interactively resolved. Please see our concerns below:

1. (b)(4)
(b)(4)

2. (b)(4)
(b)(4)

Please reply to this email confirming that you have received this request. Kindly provide your responses no later than 10am Monday, January 9, 2017. Please feel free to call or email with any questions or concerns. Many thanks!

Regards,

Binoy

Binoy Mathews
Biomedical Engineer/Lead Reviewer
Neurostimulation Devices Psychiatry Branch
Division of Neurological and Physical Medicine Devices
Center for Devices and Radiological Health
Office of Device Evaluation
U.S. Food and Drug Administration
Tel: 301-796-6475
binoy.mathews@fda.hhs.gov<mailto:binoy.mathews@fda.hhs.gov>

[cid:image001.png@01D1C57E.DFA022A0]<http://www.fda.gov/>

[cid:image002.jpg@01D1C57E.DFA022A0]<https://www.facebook.com/FDA>
[cid:image003.jpg@01D1C57E.DFA022A0] <https://twitter.com/US_FDA>
[cid:image004.jpg@01D1C57E.DFA022A0]
<http://www.youtube.com/user/USFoodandDrugAdmin>
[cid:image005.jpg@01D1C57E.DFA022A0]
<http://www.flickr.com/photos/fdaphotos/>
[cid:image006.jpg@01D1C57E.DFA022A0]

<http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/default.htm
>
Excellent customer service is important to us. Please take a moment to
provide feedback regarding the customer service you have received: click
here<https://www.research.net/s/cdrhcustomerservice?O=400&D=460&B=462&E=&
S=E>

Official Response Attached.

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Friday, January 06, 2017 10:36 AM
To: Mathews, Binoy
Subject: RE: K161328/S001

Good Morning Ben,

(b)(4)

(b)(4)

Please let me know if this response is satisfactory and if you need any additional information. As always, thanks for your help!

Best,

Nancy

Nancy Durst Clementi, M.D.
Clementi and Associates, Ltd
919 Conestoga Road
Building 3, Suite 312
Rosemont, PA 19010
610-527-2600
www.regulatoryaffairs.com

From: Mathews, Binoy [mailto:Binoy.Mathews@fda.hhs.gov]
Sent: Thursday, January 05, 2017 11:25 AM
To: Nancy Clementi <Nancy.Clementi@clempharma.net>
Subject: K161328/S001

Hi Nancy,

Happy New Year! Your 510k Supplement is currently under review. We have a few concerns which we believe can be interactively resolved. Please see our concerns below:

1. (b) (4) [redacted]

2. (b)(4) [redacted]

Please reply to this email confirming that you have received this request. Kindly provide your responses **no later than 10am Monday, January 9, 2017.** Please feel free to call or email with any questions or concerns. Many thanks!

Regards,

Binoy

Binoy Mathews
Biomedical Engineer/Lead Reviewer
Neurostimulation Devices Psychiatry Branch
Division of Neurological and Physical Medicine Devices
Center for Devices and Radiological Health
Office of Device Evaluation
U.S. Food and Drug Administration
Tel: 301-796-6475
binoy.mathews@fda.hhs.gov


cid:image001.png@01D1C
57E.DFA022A0

. . . . .

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: click here

FYI...

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Wednesday, January 11, 2017 11:49 AM
To: Mathews, Binoy
Subject: RE: K161328/S001

Good morning Binoy,

Yes, (b)(4) (b)(4) At the moment Cambridge Cognition has all of the various changes which are needed in production

Thank for your help.

Best,

Nancy

From: Mathews, Binoy [mailto:Binoy.Mathews@fda.hhs.gov]
Sent: Wednesday, January 11, 2017 11:24 AM
To: Nancy Clementi <Nancy.Clementi@clempharma.net>
Subject: RE: K161328/S001

Hi Nancy,

Thanks for sending us the revisions. I just wanted to clarify one thing with you. (b)(4) (b)(4) Kindly let me know. Thanks!

Regards,

Binoy

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Monday, January 09, 2017 9:57 AM
To: Mathews, Binoy
Subject: RE: K161328/S001

Good morning Binoy,

I wanted to send a quick note to ask if you have what you need from Cambridge Cognition. . . . . we are prepared to make any additional changes you may wish, so just let me know.

Best,

Nancy

From: Mathews, Binoy [mailto:Binoy.Mathews@fda.hhs.gov]
Sent: Thursday, January 05, 2017 11:25 AM

To: Nancy Clementi <Nancy.Clementi@clempharma.net>
Subject: K161328/S001

Hi Nancy,

Happy New Year! Your 510k Supplement is currently under review. We have a few concerns which we believe can be interactively resolved. Please see our concerns below:

1. (b)(4)
2. (b)(4)

Please reply to this email confirming that you have received this request. Kindly provide your responses **no later than 10am Monday, January 9, 2017.** Please feel free to call or email with any questions or concerns. Many thanks!

Regards,

Binoy

Binoy Mathews
Biomedical Engineer/Lead Reviewer
Neurostimulation Devices Psychiatry Branch
Division of Neurological and Physical Medicine Devices
Center for Devices and Radiological Health
Office of Device Evaluation
U.S. Food and Drug Administration
Tel: 301-796-6475
binoy.mathews@fda.hhs.gov


cid:image001.png@01D1C
57E.DFA022A0

. . . . .

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: click here

Official Response Attached.

From: Nancy Clementi [mailto:Nancy.Clementi@clempharma.net]
Sent: Friday, January 06, 2017 10:36 AM
To: Mathews, Binoy
Subject: RE: K161328/S001

Good Morning Ben,

(b)(4)

(b)(4)

Please let me know if this response is satisfactory and if you need any additional information. As always, thanks for your help!

Best,

Nancy

Nancy Durst Clementi, M.D.
Clementi and Associates, Ltd
919 Conestoga Road
Building 3, Suite 312
Rosemont, PA 19010
610-527-2600
www.regulatoryaffairs.com<http://www.regulatoryaffairs.com>

From: Mathews, Binoy [mailto:Binoy.Mathews@fda.hhs.gov]
Sent: Thursday, January 05, 2017 11:25 AM
To: Nancy Clementi
<Nancy.Clementi@clempharma.net<mailto:Nancy.Clementi@clempharma.net>>
Subject: K161328/S001

Hi Nancy,

Happy New Year! Your 510k Supplement is currently under review. We have a few concerns which we believe can be interactively resolved. Please see our concerns below:

1. (b)(4)
(b)(4)

2. In response to Deficiency #5, you have revised your labeling and
(b)(4)

Please reply to this email confirming that you have received this request. Kindly provide your responses no later than 10am Monday, January 9, 2017. Please feel free to call or email with any questions or concerns. Many thanks!

Regards,

Binoy

Binoy Mathews
Biomedical Engineer/Lead Reviewer
Neurostimulation Devices Psychiatry Branch
Division of Neurological and Physical Medicine Devices
Center for Devices and Radiological Health
Office of Device Evaluation
U.S. Food and Drug Administration
Tel: 301-796-6475
binoy.mathews@fda.hhs.gov<mailto:binoy.mathews@fda.hhs.gov>

[cid:image001.png@01D1C57E.DFA022A0]<http://www.fda.gov/>

[cid:image002.jpg@01D1C57E.DFA022A0]<https://www.facebook.com/FDA>
[cid:image003.jpg@01D1C57E.DFA022A0] <https://twitter.com/US_FDA>
[cid:image004.jpg@01D1C57E.DFA022A0]
<http://www.youtube.com/user/USFoodandDrugAdmin>
[cid:image005.jpg@01D1C57E.DFA022A0]
<http://www.flickr.com/photos/fdaphotos/>
[cid:image006.jpg@01D1C57E.DFA022A0]
<http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/default.htm
>
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: click here<https://www.research.net/s/cdrhcustomerservice?O=400&D=460&B=462&E=&S=E>

July 15, 2016</br></br> We have reviewed your submission K161328 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, referencing the submission number K161328 to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please refer to the eCopy guidance at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf for current information on the number of copies and the format (paper versus eCopy) you must submit.

Your response is due within 180 days from the date of this request, which is January 11, 2017. If a complete response is not received in CDRH's Document Control Center within 180 days, we will consider this submission to be withdrawn, and we will delete it from our review system.

You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission to the Document Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.

Should you have questions about this email, you may contact Binoy Mathews, the lead reviewer assigned to your submission.

 *** This is a system-generated email notification ***

May 26, 2016</br></br>
Acceptance Review Notification - Accepted

An administrative acceptance review was conducted on your premarket notification (510(k)) K161328, and it was found to contain all of the necessary elements and information needed to proceed with the substantive review. We will contact you should we require any additional information during the course of the substantive review. The lead reviewer assigned to your submission is Binoy Mathews.

 *** This is a system-generated email notification ***

January 13, 2017</br></br> We have completed our review. Please refer to the attached letter for details.

If you have any questions, please contact the lead reviewer assigned to your submission, Binoy Mathews.

 *** This is a system-generated email notification ***

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

K161328
Cambridge Cognition Ltd., Us Agent: Clementi Associates Ltd.
Device Trade Name: Cantab Mobile
Contact Name: Nancy Clementi

DEFICIENCY LIST

Substantial Equivalence Discussion

1. You have identified the AnthroTronix – DANA (K141865) as the primary predicate device for comparison to the Cantab Mobile for the purposes of establishing substantial equivalence. The DANA indications for use state that it "provides clinicians with objective measurements of reaction time (speed and accuracy) to aid in the assessment of an individual's medical or psychological state. DANA also delivers and scores standardized psychological questionnaires"). In comparison, the Cantab Mobile seeks to be indicated "for the assessment of memory in adult individuals aged 50 to 90 years of age." The device also specific in that it is "indicated to provide clinicians with objective measurements of visuospatial episodic memory and mood."

   Reaction Time and Memory are two distinct cognitive processes which are used to assess different aspects of cognition. Therefore, the predicate device you have chosen is not appropriate. Please select a predicate device whose intended use is similar to the Cantab Mobile and revise your application accordingly. We believe it is appropriate for you to consider using DEN130033 (Cerebral Assessment Systems, Inc. – Cognivue) or K150154 (Vista Lifesciences – ANAM Test System) as potential predicate devices as these devices are indicated as computerized adjunctive assessments of memory. However, please note that you will need to provide a detailed comparison to the new predicate device, and where differences exist, information to support how Cantab Mobile can be considered equivalent. For example, while considering these predicates please keep in mind that these testing systems use multiple tests to produce an outcome; you would need to support the use of the PAL as a single test used to assess memory in comparison to these predicates which test memory in multiple domains. Additionally, it is important to provide evidence that the PAL may be used without an assessment of baseline function in the proposed use and that decrements cited as severe are outside the range that could attributed to normal aging.

Indications for Use

2. Your Indications for Use Statement states that the Cantab Mobile will be used to assess memory in patients aged 50 to 90 years. The assessment of memory is a broad term and your Indications for Use should specify the type of memory that is being assessed in order to provide the user with an accurate description of the purpose of the device. Since the Cantab Mobile will use the PAL test to make its assessment of visuospatial learning, please revise your Indications for Use Statement to "assess visuospatial associative learning in patients aged 50 to 90 years."

Device Description

3. Within your Executive Summary and Device Labeling, you make multiple references to specific conditions such as Mild Cognitive Impairment and Dementia and state that the Cantab Mobile can detect memory impairment in such individuals. Please note that indicating your device for "assessment of memory in adult individuals aged 50 to 90 years of age" is different from making claims related to specific disease states; test scores resulting in this outcome may be attributed to other causes and patients should be referred for clinical evaluation. Indicating your device for MCI or Dementia would constitute a new intended use which would need to be reviewed via the DeNovo pathway due to lack of a suitable predicate. Therefore, please revise your Executive Summary, Device Results, and labeling by removing the reference to MCI or Dementia. In addition, please include a statement that the results of the Cantab Mobile should only be interpreted by a qualified professional.

4. You state that the Cantab Mobile includes the optional administration of the Geriatric Depression Screening Questionnaire (GDS) and the Activities for Daily Living Questionnaire (ADL). If administered, you mention that scores will be presented to the clinician. Please address the following items related to these questionnaires:

   a. (b) (4)

   b. In addition, please verify if the GDS and ADL Questionnaires are consistent with the published, validated versions. If not, please cite the versions used and provide literature to support their clinical use.

   c. (b) (4)

(b) (4)

(b) (4)

[redacted]

Software

(b) (4)

[redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K161328

Device Name
CANTAB Mobile

Indications for Use *(Describe)*
The CANTAB Mobile is intended to be used as an adjunctive tool to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

January 13, 2017

Cambridge Cognition Ltd.,
% Nancy Clementi, MD
Chief Medical Officer, Clementi Associates Ltd.
Clementi Associates Ltd
919 Conestoga Rd, Building 3, Suite 312
Rosemont, Pennsylvania 19010

Re: K161328
Trade/Device Name: Cantab Mobile
Regulation Number: 21 CFR 882.1470
Regulation Name: Computerized Cognitive Assessment Aid
Regulatory Class: Class II
Product Code: PKQ
Dated: December 21, 2016
Received: December 21, 2016

Dear Dr. Clementi:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in

the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

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Sincerely yours,

Michael J. Hoffmann -S

for Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

January 13, 2017

Cambridge Cognition Ltd.,
% Nancy Clementi, MD
Chief Medical Officer, Clementi Associates Ltd.
Clementi Associates Ltd
919 Conestoga Rd, Building 3, Suite 312
Rosemont, Pennsylvania 19010

Re: K161328
Trade/Device Name: Cantab Mobile
Regulation Number: 21 CFR 882.1470
Regulation Name: Computerized Cognitive Assessment Aid
Regulatory Class: Class II
Product Code: PKQ
Dated: December 21, 2016
Received: December 21, 2016

Dear Dr. Clementi:

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Sincerely yours,

Michael J. Hoffmann -S

for Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K161328

Device Name
CANTAB Mobile

Indications for Use *(Describe)*
The CANTAB Mobile is intended to be used as an adjunctive tool to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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CAMBRIDGE COGNITION

April 08, 2016

Premarket Notification
510(k) Statement
As Required by
21 CFR 807.93]

Original 510(k) Submission
Cantab Mobile

(As Required By 21 CFR 807.93)
I certify that, in my capacity as Director of Technical Operations of Cambridge Cognition Ltd., I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61.

(Signature of Certifier)

Ricky Dolphin

(Typed Name)

08-APR-2016

(Date)

Cambridge Cognition Tunbridge Court, Tunbridge Lane, Bottisham, Cambridge, CB25 9TU, UK
t: +44 (0)1223 810700 f: +44 (0)1223 810701 info@camcog.com www.cambridgecognition.com

Cambridge Cognition Holdings plc, a company registered in England and Wales, Registered Number 04338746

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

K161328
Cambridge Cognition Ltd., Us Agent: Clementi Associates Ltd.
Device Trade Name: Cantab Mobile
Contact Name: Nancy Clementi

DEFICIENCY LIST

Substantial Equivalence Discussion

1. You have identified the AnthroTronix – DANA (K141865) as the primary predicate device for comparison to the Cantab Mobile for the purposes of establishing substantial equivalence. The DANA indications for use state that it "provides clinicians with objective measurements of reaction time (speed and accuracy) to aid in the assessment of an individual's medical or psychological state. DANA also delivers and scores standardized psychological questionnaires"). In comparison, the Cantab Mobile seeks to be indicated "for the assessment of memory in adult individuals aged 50 to 90 years of age." The device also specific in that it is "indicated to provide clinicians with objective measurements of visuospatial episodic memory and mood."

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   a. (b) (4)

   b. In addition, please verify if the GDS and ADL Questionnaires are consistent with the published, validated versions. If not, please cite the versions used and provide literature to support their clinical use.

   c. (b) (4)

(b) (4)

(b) (4)

Software

(b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K161328

Device Name
CANTAB Mobile

Indications for Use *(Describe)*
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

January 13, 2017

Cambridge Cognition Ltd.,
% Nancy Clementi, MD
Chief Medical Officer, Clementi Associates Ltd.
Clementi Associates Ltd
919 Conestoga Rd, Building 3, Suite 312
Rosemont, Pennsylvania 19010

Re: K161328
Trade/Device Name: Cantab Mobile
Regulation Number: 21 CFR 882.1470
Regulation Name: Computerized Cognitive Assessment Aid
Regulatory Class: Class II
Product Code: PKQ
Dated: December 21, 2016
Received: December 21, 2016

Dear Dr. Clementi:

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Sincerely yours,

Michael J. Hoffmann -S

for Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Department of Health & Human Services
Food and Drug Administration

Center for Devices and Radiological Health
Office of Device Evaluation & Office of In-Vitro Diagnostics and Radiological Health

Contains Nonbinding Recommendations

Print Form

Acceptance Checklist for Traditional 510(k)s

(Should be completed within 15 days of DCC receipt)

The following information is not intended to serve as a comprehensive review.
FDA recommends that the submitter include this completed checklist as part of the submission.

510(k) #: K161328 Date Received by DCC: May 12, 2016

Lead Reviewer: Binoy Mathews

Branch: NSDB Division: DNPMD Center/Office: CDRH/ODE

Note: If an element is left blank on the checklist, it does not mean the checklist is incomplete; it means the reviewer did not assess the element during the RTA review and that the element will be assessed during substantive review.

IMPORTANT - Many checklist elements include additional details regarding information to address the element that can be seen by hovering over the element (Example - Element 4 in Section A of the checklist).

Preliminary Questions

Answers in the shaded blocks indicate consultation with a Center advisor is needed. (Boxes checked in this section represent FDAs preliminary assessment of these questions at the time of administrative review.)	Yes	No	N/A
1) Is the product a device (per section 201(h) of the FD&C Act) or a combination product (per 21 CFR 3.2(e)) with a device constituent part subject to review in a 510(k)? If it appears not to be a device (per section 201(h) of the FD&C Act) or such a combination product, or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Product Jurisdiction Liaison to determine the appropriate action, and inform division management. *Provide a summary of the Jurisdictional Officer's/Liaison's determination.* If the product does not appear to be a device or such a combination product, mark "No."	X		
Comments:			
2. Is the submission with the appropriate Center? If the product is a device or a combination product with a device constituent part, is it subject to review by the Center in which the submission was received? If you believe the submission is not with the appropriate Center or you are unsure, consult with the CDRH Jurisdictional Officer or CBER Product Jurisdiction Liaison to determine the appropriate action and inform your division management. *Provide a summary of the Jurisdictional Officer's/Liaison's determination.* If submission should not be reviewed by your Center mark "No."	X		
Comments:			
3) If a Request for Designation (RFD) was submitted for the device or combination product with a device constituent part and assigned to your center, identify the RFD # and confirm the following: **a) Is the device or combination product the same (e.g., design, formulation) as that presented in the RFD submission?** **b) Are the indications for use for the device or combination product identified in the 510(k) the same as those identified in the RFD submission?** If you believe the product or the indications presented in the 510(k) have changed from the RFD, or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Product Jurisdiction Liaison to determine the appropriate action and inform your division management. *Provide summary of Jurisdictional Officer's/Liaison's determination.* If the answer to either question above is no, mark "No." If there was no RFD, mark "N/A."			X
Comments:			

4) Is this device type eligible for a 510(k) submission? If a 510(k) does not appear to be appropriate (e.g., Class III type and PMA required, or Class I or II type and 510(k)-exempt), you should consult with the CDRH 510(k) Program Director or appropriate CBER staff during the acceptance review. If 510(k) is not the appropriate regulatory submission, mark "No."	X		
Comments:			
5) Is there a pending PMA for the same device with the same indications for use? If yes, consult division management and the CDRH 510(k) Program Director or appropriate CBER staff to determine the appropriate action.		X	
Comments:			
6) If clinical studies have been submitted, is the submitter the subject of an Application Integrity Policy (AIP)? If yes, consult with the CDRH Office of Compliance/Division of Bioresearch Monitoring (OC/DBM) or CBER Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Bioresearch Monitoring Branch (OCBQ/DIS/BMB) to determine the appropriate action. Check on web at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm If no clinical studies have been submitted, mark "N/A."		X	
Comments:			

- If the answer to 1 or 2 appears to be "No," then stop review of the 510(k) and issue the "Original Jurisdictional Product" letter.
- If the answer to 3a or 3b appears to be "No," then stop the review and contact the CDRH Jurisdictional Officer or CBER Office of Jurisdiction Liaison.
- If the answer to 4 is "No," the lead reviewer should consult division management and other Center resources to determine the appropriate action.
- If the answer to 5 is "Yes," then stop review of the 510(k), contact the CDRH 510(k) Staff and PMA Staff, or appropriate CBER staff.
- If the answer to 6 is "Yes," then contact CDRH/OC/DBM or CBER/OCBQ/DIS/BMB, provide a summary of the discussion with DBM or BMB Staff, and indicate their recommendation/action.

Organizational Elements

Failure to include these items should not result in an RTA designation.

*Submitters including the checklist with their submission should identify the page numbers where requested information located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	*Page #
1) Submission contains a Table of Contents	X		
2) Each section is labeled (e.g., headings or tabs designating Device Description section, Labeling section, etc.)	X		
3) All pages of the submission are numbered.	X		
4) Type of 510(k) is identified (i.e., Traditional, Abbreviated, or Special).	X		
Comments:			

Elements of a Complete Submission (RTA Items)

(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed.

- Any "No" answer will result in a "Refuse to Accept" decision; however, FDA staff has discretion to determine whether missing items are needed to ensure that the submission is administratively complete to allow the submission to be accepted or to request missing checklist items interactively from submitters during RTA review.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
A. Administrative					
1) All content used to support the submission is written in English (including translations of test reports, literature articles, etc.)	X				
2) Submission identifies the following (FDA recommends use of the CDRH Premarket Review Submission Cover Sheet form [Form 3514]):					
a) Device trade/proprietary name	X				
b) Device class and panel or Classification regulation or Statement that device has not been classified with rationale for that conclusion	X				
3) Submission contains an Indication for Use Statement with Rx and/or OTC designated (see also 21 CFR 801.109, and FDA's guidance "Alternative to Certain Prescription Devices Labeling Requirements.") *See recommended format.* *(http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM360431.pdf).*	X				
4) Submission contains a 510(k) Summary or 510(k) Statement.	X				
5) Submission contains a Truthful and Accuracy Statement per 21 CFR 807.87(k) *See recommended format.* *(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142707.htm).*	X				
6) Submission is a Class III 510(k) device.			X		
7) Submission contains clinical data	X				
a) Submission includes completed Financial Certification (FDA Form 3454) or Disclosure (FDA Form 3455) information for each covered clinical study included in the submission. *Select "N/A" if the submitted clinical data is not a "covered clinical study" as defined in the Guidance for Industry- Financial Disclosures by Clinical Investigators.*			X		
b) Submission includes completed Certification of Compliance with requirements of ClinicalTrials.gov Data Bank (FDA Form 3674) (42 U.S.C. 282(j)(5)(B)) for each applicable device clinical trial included in the submission. *Select "N/A" if the submitted clinical data is not an "applicable device clinical trial" as defined in Title VIII of FDAAA, Sec. 801(j)*			X		
8) The submission identifies prior submissions for the same device included in the current submission (e.g., submission numbers for a prior not substantially equivalent [NSE] determination, prior deleted or withdrawn 510(k), Pre-Submission, IDE, PMA, etc.). **OR** States that there were no prior submissions for the subject device.	X				
a) If there were prior submissions, the submitter has identified where in the current submission any issues related to a determination of substantial equivalence from prior submissions for this device are addressed.			X		
B. Device Description					
9) The device has a device-specific guidance document, special controls document, and/or requirements in a device-specific regulation regarding device description that is applicable to the subject device.	X				

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
a) The submission addresses device description recommendations outlined in the device-specific guidance. **OR** The submission provides an alternative approach intended to address the applicable statutory and/or regulatory criteria.			X		
b) The submission includes device description information that addresses relevant mitigation measures set forth in a special controls document or device-specific regulation applicable to the device. **OR** The submission uses alternative mitigation measures and provides rationale why the alternative measures provide an equivalent assurance of safety and effectiveness.			X		
10) Descriptive information is present and consistent within the submission (e.g., the device description section is consistent with the device description in the labeling).	X				
11) The submission includes descriptive information for the device, including the following:					
a) A description of the principle of operation or mechanism of action for achieving the intended effect.	X				
b) A description of proposed conditions of use, such as surgical technique for implants; anatomical location of use; user interface; how the device interacts with other devices; and/or how the device interacts with the patient.	X				
c) A list and description of each device for which clearance is requested.	X				
d) Submission contains representative engineering drawing(s), schematics, illustrations, photos and/or figures of the device. **OR** Submission includes a statement that engineering drawings, schematics, etc. are not applicable to the device (e.g., device is a reagent and figures are not pertinent to describe the device).	X				
12) Device is intended to be marketed with multiple components, accessories, and/or as part of a system.			X		
C. Substantial Equivalence Discussion					
13) Submitter has identified a predicate device(s), including the following information:					
a) Predicate device identifier provided (e.g., 510(k) number, de novo number, reclassified PMA number, regulation number if exempt or statement that the predicate is a preamendment device). For predicates that are preamendments devices, information is provided to document preamendments status. *Information regarding documenting preamendment status is available online. (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/MedicalDeviceQualityandCompliance/ucm379552.htm).*	X				
b) The identified predicate(s) is consistent throughout the submission (e.g., the predicate(s) identified in the Substantial Equivalence section is the same as that listed in the 510(k) Summary (if applicable) and that used in comparative performance testing).	X				

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
14) Submission includes a comparison of the following for the predicate(s) and subject device and a discussion why any differences between the subject and predicate(s) do not impact safety and effectiveness [see section 513(i)(1)(A) of the FD&C Act and 21 CFR 807.87(f)] *See "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" guidance document for more information on comparing intended use and technological characteristics.*					
a) Indications for Use	X				
b) Technology, including features, materials, and principles of operation	X				
D. Proposed Labeling (see also 21 CFR part 801 and 809 as applicable)					
15) Submission includes proposed package labels and labeling (e.g., instructions for use, package insert, operator's manual).	X				
a) Indications for use are stated in labeling and are identical to Indications for Use form and 510(k) Summary (if 510(k) Summary provided).	X				
b) Labeling includes: - Statements of conditions, purposes or uses for which the device is intended (e.g., hazards, warnings, precautions, contraindications) (21 CFR 801.5) **AND** - Includes adequate directions for use (see 21 CFR 801.5) **OR** - Submission states that device qualifies for exemption per 21 CFR 801 Subpart D	X				
16) Labeling includes name and place of business of the manufacturer, packer, or distributor (21 CFR 801.1).	X				
17) Labeling includes the prescription statement [see 21 CFR 801.109(b)(1)] or Rx Only symbol (see also Section 502(a) of the FD&C Act and FDA's guidance "Alternative to Certain Prescription Device Labeling Requirements").	X				
18) The device has a device-specific guidance document, special controls document, and/or requirements in a device-specific regulation regarding labeling that is applicable to the subject device.			X		
19) If the device is an in vitro diagnostic device, provided labeling includes all applicable information required per 21 CFR 809.10.			X		
E. Sterilization					
If an *in vitro* diagnostic (IVD) device and sterilization is not applicable, select "N/A." The criteria in this section will be omitted from the checklist if "N/A" is selected.			X		
F. Shelf Life					
24) Proposed shelf life/expiration date stated **OR** Statement that shelf-life is not applicable because of low likelihood of time-dependent product degradation	X				
25) For a sterile device, submission includes summary of methods used to establish that device packaging will maintain a sterile barrier for the entirety of the proposed shelf life.			X		

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
26) Submission includes summary of methods used to establish that device performance is maintained for the entirety of the proposed shelf-life (e.g., mechanical properties, coating integrity, pH, osmolality, etc.). **OR** Statement why performance data is not needed to establish maintenance of device performance characteristics over the shelf-life period.	X				
G. Biocompatibility					
If an vitro diagnostic (IVD) device, select "N/A." The criteria in this section will be omitted from the checklist if "N/A" is selected.					
Submission states that there: (one of the below must be checked)					
	Are direct or indirect patient-contacting components.				
X	Are no direct or indirect patient-contacting components.				
	Information regarding patient contact status of the device is not provided (if this box checked, please also check one of the two boxes below).				
	Patient contact information not needed for this device (e.g., software-only device)				
	Patient contact information needed or need unclear				
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
H. Software					
Submission states that the device: (one of the below must be checked)					
X	Does contain software/firmware				
	Does not contain software/firmware				
	Information on whether device contains software/firmware is not provided. (If this box is checked, please also check one of the two boxes below.)				
	Software/firmware information not needed for this device (e.g., surgical suture, condom)				
	Software/firmware information is needed or need unclear				
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
30) Submission includes a statement of software level of concern and rationale for the software level of concern.	X				
31) All applicable software documentation provided based on level of concern identified by the submitter, as described in Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, or the submission includes information to establish that the submitter has otherwise met the applicable statutory or regulatory criteria through an alternative approach (i.e., the submitter has identified an alternate approach with a rationale).		X		X	
Comments:	You have not provided software documentation per the mentioned Guidance Document according to the level of concern of your software. Please include all required documents per the designated level of concern. WILL INTERACTIVELY REQUEST THIS INFORMATION.				
I. Electrical Safety and EMC					

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
Electrical Safety Submission states that the device: (one of the below must be checked)					
	Does require electrical safety evaluation				
X	Does not require electrical safety evaluation				
	Information on whether device requires electrical safety evaluation is not provided. (If this box is checked, please also check one of the two boxes below.)				
	Electrical safety information not needed for this device (e.g., surgical suture, condom)				
	Electrical safety information is needed or need unclear				
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
EMC Submission states that the device: (one of the below must be checked)					
	Does require EMC evaluation				
X	Does not require EMC evaluation				
	Information on whether device requires EMC evaluation is not provided. (If this box is checked, please also check one of the two boxes below.)				
	EMC information not needed for this device (e.g., surgical suture, condom)				
	EMC information is needed or need unclear				
This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.					
J. Performance Data - General					
If an in vitro diagnostic (IVD) device, select "N/A." The criteria in this section will be omitted from checklist if "N/A" is selected. Performance data criteria relating to IVD devices is addressed in Section K.					
34) Full test report is provided for each completed test. A full test report includes: objective of the test, description of the test methods and procedures, study endpoint(s), pre-defined pass/fail criteria, results summary, conclusions.	X				
a) Submission includes an explanation of how the data generated from each test report supports a finding of substantial equivalence (e.g., comparison to predicate device testing, dimensional analysis, etc.).	X				
35) The device has a device-specific guidance document, special controls document, and/ or requirements in a device-specific regulation regarding performance data that is applicable to the subject device.			X		
36) If literature is referenced in the submission, submission includes:					
a) Legible reprints or a summary of each article.	X				
b) Discussion of how each article is applicable to support the substantial equivalence of the subject device to the predicate.	X				
37) For each completed animal study, the submission provides the following:			X		
K. Performance Characteristics - In Vitro Diagnostic Devices Only **(Also see 21 CFR 809.10(b)(12))**					

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. *Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.	Yes	No	N/A	Comment	*Page #
Submission states that the device: (one of the below must be checked)					
	is an in vitro diagnostic device.				
X	is not an in vitro diagnostic device.				
If "is not" is selected, the performance data-related criteria below are omitted from the checklist.					

Decision: (•) Accept ( ) Refuse to Accept

If Accept, notify applicant.

If Refuse to Accept, notify applicant electronically and include a copy of this checklist.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Binoy J. Mathews -S 2016.05.26 09:57:45 -04'00'
Branch Chief Sign-Off (digital signature optional)*	
Division Sign-Off (digital signature optional)*	

* Branch and Division review of checklist and concurrence with decision required. Branch and Division digital signature optional.

Tinch, Latroy D

From: Marjenin, Timothy
Sent: Friday, July 15, 2016 10:46 AM
To: Mathews, Binoy; Shenouda, Christian; Gupta, Jay
Subject: RE: K161328 AINN [SI goal - 7/11]

Thanks to all of you for the edits and clarifications. I'll be logging this out shortly, and uploading this email chain to DocMan to serve as documentation of the additional discussion that has transpired.

Aside from some additional grammatical and formatting revisions I'll be making to the deficiencies, the most substantive change will be to the following deficiency:

(b)(4)

Tim

Tim Marjenin
Branch Chief, Neurostimulation Devices Branch
Division of Neurological and Physical Medicine Devices
[FDA/CDRH/ODE/DNPMD/NSDB]

Would you like to provide feedback on my customer service? Click here!

From: Mathews, Binoy
Sent: Thursday, July 14, 2016 9:43 AM
To: Shenouda, Christian; Gupta, Jay; Marjenin, Timothy
Subject: RE: K161328 AINN [SI goal - 7/11]
Importance: High

Hi All,

Added some language and an additional deficiency to our AINN Letter. Kindly review and let me know if there are concerns. Thanks!

--Binoy

From: Shenouda, Christian
Sent: Wednesday, July 13, 2016 4:07 PM
To: Gupta, Jay; Marjenin, Timothy
Cc: Mathews, Binoy
Subject: RE: K161328 AINN [SI goal - 7/11]

Hi Jay,

We have reviewed the CANTAB submission and your comments below.

(b)(4)

Thanks,
Christian

From: Gupta, Jay
Sent: Tuesday, July 12, 2016 6:13 PM
To: Marjenin, Timothy; Mathews, Binoy; Shenouda, Christian
Subject: RE: K161328 AINN [SI goal - 7/11]

Hello folks!

I have some additional high-level context regarding Tim's points below that may be helpful:

(b)(4)

(b)(4)

Let me know if additional clarification/discussion is needed. I will be available via email late-night tomorrow and potentially by phone (631-335-8708) at spotty/unknown times on Thursday and Friday. If you are trying to reach me by phone, please just leave a message or a text and I'll get back to you if/when I can.

Thanks,
Jay

Jay Gupta, M.S.E.
Senior Reviewer (Detail)
Neurostimulation Devices Branch (NSDB)
Division of Neurological and Physical Medicine (DNPMD)
FDA/CDRH/ODE
Phone #: (301) 796-2795
E-mail: jay.gupta@fda.hhs.gov

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From: Marjenin, Timothy
Sent: Tuesday, July 12, 2016 5:06 PM

To: Mathews, Binoy; Shenouda, Christian; Gupta, Jay
Subject: RE: K161328 AINN [SI goal - 7/11]

Thanks for the updates! I took some more time to go through the memos and the deficiencies again, and I still have a few questions. This includes a couple that I hadn't identified at first since I hadn't gone over the memos as thoroughly.

For the attached deficiencies, I've accepted everything that is good to go. I've included Jay on this email due to his familiarity with these devices; he can provide some high-level input, though not after tomorrow. The additional questions revolve primarily around the following:

(b)(4)

[redacted]

Tim

Tim Marjenin
Branch Chief, Neurostimulation Devices Branch
Division of Neurological and Physical Medicine Devices
[FDA/CDRH/ODE/DNPMD/NSDB]

Would you like to provide feedback on my customer service? Click here!

From: Mathews, Binoy
Sent: Tuesday, July 12, 2016 2:27 PM
To: Shenouda, Christian; Marjenin, Timothy
Subject: RE: K161328 AINN [SI goal - 7/11]

Hi Tim,

We have addressed your comments and they are attached. Please Let me know if you have any questions.

Christian – Did I forget to convey any of your deficiencies? I did not think Tim's point below was meant to convey as a deficiency, but if it did please let me know. I would need to better understand what you wanted to convey.

Thanks!

--Binoy

From: Shenouda, Christian
Sent: Monday, July 11, 2016 5:23 PM
To: Mathews, Binoy
Subject: FW: K161328 AINN [SI goal - 7/11]
Importance: High

Hi,

Attached are my edits.

(b)(4)

Thanks,
Christian

From: Marjenin, Timothy
Sent: Monday, July 11, 2016 3:13 PM
To: Mathews, Binoy; Shenouda, Christian
Subject: RE: K161328 AINN [SI goal - 7/11]
Importance: High

In addition to the edits to the deficiencies, some additional comments:

(b)(4)

Tim

Tim Marjenin
Branch Chief, Neurostimulation Devices Branch
Division of Neurological and Physical Medicine Devices
[FDA/CDRH/ODE/DNPMD/NSDB]

Would you like to provide feedback on my customer service? Click here!

From: Mathews, Binoy
Sent: Monday, July 11, 2016 1:53 PM
To: Marjenin, Timothy

Subject: FW: K161328 AINN [SI goal - 7/11]
Importance: High

Hi Tim,

I just wanted to remind you about this SI goal. Let me know if you have any questions. Thanks!

--Binoy

From: Mathews, Binoy
Sent: Friday, July 08, 2016 1:20 PM
To: Marjenin, Timothy
Cc: Shenouda, Christian
Subject: K161328 AINN [SI goal - 7/11]

Hi Tim,

SI review of K161328 is complete. The subject device is a software based memory assessment tool called the Cantab Mobile. We are recommending AINN requesting the sponsor to select a more appropriate predicate device and provide the necessary information to support substantial equivalence to the new predicate. Kindly review our deficiencies and edit where necessary. Thanks!

Documents:
http://docs.fda.gov/share/page/site/submissions/documentlibrary#filter=path%7C%2FReviews%2F510%2528k%2529s%2F2016%2F1201%2520-%25201400%2FK161328%2FReviewer%2520Documents%7C&page=1

--Binoy

Binoy Mathews
Biomedical Engineer | Neurostimulation Devices Branch
DNPMD/CDRH/FDA | WO66 Room 2622
10903 New Hampshire Avenue | Silver Spring, MD 20993-0002
Phone: 301-796-6475
e-mail: binoy.mathews@fda.hhs.gov

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FOOD AND DRUG ADMINISTRATION MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
White Oak, MD 20993

510(k) MEMORANDUM
Medical Officer Review

Date: June 20, 2016
To: Binoy Mathews, PhD - DNPMD Office: ODE
From: Christian Shenouda, MD - DNPMD

Device Name: Cantab Mobile
Sponsor: CAMBRIDGE COGNITION LTD

RECOMMENDATION

There are questions regarding Substantial Equivalance (SE) to the listed predicate device given that the devices measure disparate cognitive domains.
Additionally, proposed IFU should be revised to reflect the specific memory domain assessed.

SUMMARY

This is a consult for a clinical review of a 510(k) submission K161328, the CANTAB Mobile Device intented to assess memory in adults age 50 – 90. The specific memory domain tested is visuospatial memory via usage of the CANTAB PAL test. This test has been used with other tests to identify early cognitive decline but is presented here as the sole assessment. The sponsor has identified a predicate device which assesses a separate cognitive domain, raising concern that the devices are NSE. The sponsor may wish to cite an alternate device such as the ANAM or Cognivue which also assess memory. Should the sponsor choose this option, they should be mindful that these devices utilize multiple tests to formulate output in the assessment of the cognitive domain.

REVIEW

Clinical Background

Current criteria for the diagnosis of probable AD stipulates deterioration in two or more areas of cognition including memory of sufficient magnitude to interfere with work or social function. Critically however, substantial neuropathological change may have occurred before clinically significant symptoms (Jack et al. 2010; Jansen et al. 2015) appear. Thus, commencing treatment of AD at the time of clinical diagnosis (whether with cholinergic / glutamatergic drugs, anti-amyloid deposit agents or other putative disease modifying agents) may be sub-optimal or even ineffective because of the advanced stage of neurodegeneration at that time. The identification of cognitive tests that are sensitive to early pathological changes would facilitate the diagnosis of patients in a 'prodromal' state (i.e., those in whom the pathological process is present but whose symptoms are currently sub-clinical). Such early detection would serve to maximize the potential therapeutic benefit of treatment, enhance patient quality of life and, in so doing, reduce the burden on residential and nursing care services.
The CANTAB (Cambridge Neuropsychology Test Automated Battery) PAL (Paired Associates Learning) requires patients to learn and remember abstract visual patterns associated with various locations on a touch sensitive computer screen.

A series of independent studies have demonstrated that Cantab PAL measures of visuospatial associative learning and semantic memory are sensitive in detecting the earliest signs of prodromal Alzheimer's disease (up to 32 months prior to clinical diagnosis) both in memory clinic attendees (Fowler et al., 1995, Fowler et al., 1997; Fowler et al., 2002; Swainson et al., 2001; Blackwell et al., 2004) and in community dwelling cohorts of individuals classified as asymptomatic using current clinical measures (De Jager et al., 2002); De Jager et al., 2005).

Reviewer's comments:
The rationale for the device is adequate. (b)(4)
(b)(4)

Device Description

Cantab Mobile provides an optional patient self-assessment of memory (Self Assess - enabled on the data entry screen). If this assessment is enabled, the patient will rate his/her memory prior to taking Cantab PAL. The patient is presented a rating scale against which they rate their memory as above average (left of center), average (center), or below average (right of center). Comparing self-rated memory with the objective measure of memory, provided by Cantab PAL, can reveal any discrepancies between actual and perceived memory ability.

The Cantab Mobile memory test is based on the Cantab PAL test previously used on other hardware platforms. The Cantab PAL requires patients to learn and remember abstract visual patterns associated with various locations on a touch-sensitive computer screen. The patterns were all created to be bold, brightly colored, abstract and with no cultural context.
Patterns are presented in six boxes around the edge of the screen (See Figure 3). The patterns disappear from the screen, leaving empty boxes and, after a brief delay, the same patterns are presented sequentially in the middle of the screen and the patient is required to touch the box in which they previously saw that pattern appear.
If the patterns' locations are not recalled correctly, this is identified to the patient via audio prompts and pattern presentation and recall is repeated. This process continues until the task is completed successfully, at which point the next task is started, or repeated failures by the patient to recall the locations correctly cause the test to end. The whole test consists of a series of such tasks with increasing levels of difficulty.
The patient's responses are recorded by screen touches. The number of errors that they make are recorded and their performance is graded using algorithms derived from a normative database of around 4,000 individuals collected during academic research in the UK, taking into account their age, gender and level of education.

Cantab Mobile additionally includes optional questionnaires. Questionnaires operate by presenting a series of questions to the patient, with clearly labeled response boxes that the patient may touch in order to answer each question. Ratings scales administered (depending on patient performance, and if not disabled by the healthcare professional) comprise:

1.GDS – Geriatric Depression Screening Questionnaire
2.ADL – Activities for Daily Living Questionnaire

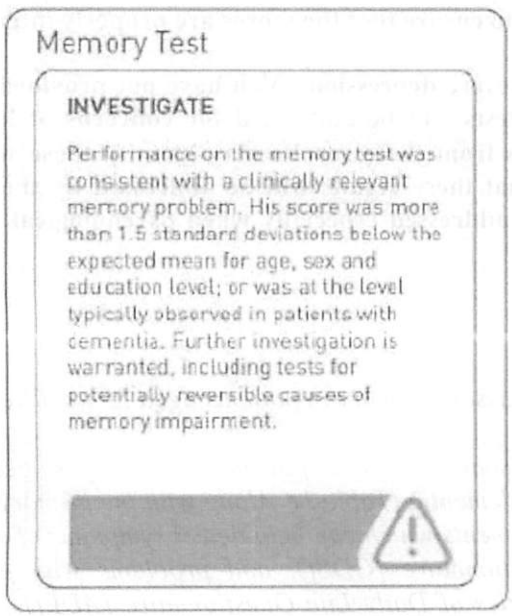
The GDS rating scale in the app is the shorter version of GDS including 15 questions, the GDS-15 (Almeida and Almeida 1999), which is based on the GDS described by Yesavage and colleagues

(Yesavage et al 1983): The GDS rating scale comprises a series of questions, each presented in turn textually on the screen using the language in force, two buttons below to allow the patient to respond 'yes' and 'no' (or equivalent in the language in force). A progress bar gives an approximate indication of progress through the questions and a button with a backward arrow allows the user to return to the preceding question (if any) and choose again. See Figure 5 below for an example of a GDS-15 rating scale question and its format, as it is presented in the app.

Administration of the ADL rating scale comprises a series of questions, each presented in turn textually on the screen using the language in force3, with the introductory text given above the question and buttons below to allow the patient to choose from the responses permitted for the question. A progress bar gives an approximate indication of progress through the questions and a button with a backward arrow allows (except on questions 1 and 11)the user to return to the preceding question and choose again.
At the conclusion of the test, a 'thank you' screen is displayed with no information on test outcome. The device holds patient report data, prior to its transfer to the practitioner's systems. It is accessible to the healthcare professional via the Report Manager.
Memory test results are presented as one of three categories, based on a combination of neuropsychological best practice and the known sensitivity and specificity of the test in detecting early Alzheimer's disease. The patient's memory test outcome takes into account the performance of individuals closely matched to the patient for age, gender and education level. It may reflect the test's ending early in order to prevent undue distress to patients making a high number of errors. The following outcome categories are reported:

***Investigate** or **Red** means that patient performance may indicate a clinically-significant memory impairment (MCI or dementia). A patient will receive a red score if:*

- *Their test score was more than 1.5 standard deviations below the mean for people of their age, sex and educational level*
- *They made more than 20 errors in the 6-pattern stage,*
- *Or they made several errors in the easier stages of the test*



***Monitor** or **Amber** means that the patient's memory is in the lower end of the normal range. This patient may benefit from additional assessment or monitoring over time.*

- A patient will receive an orange score if they score between 1 and 1.5 standard deviations below the expected level for someone of their age, sex and educational level.

***No Present Concern** or **Green** means that the patient's memory appears normal at present.*

- A patient will receive a green score if they score no more than one standard deviation below the expected level for someone of their age, sex and educational level.

If the patient falls in the Monitor or No Present Concern category then the results will also show the number of errors made at the six-pattern stage.

The report also includes information on the patient's responses in the questionnaires, if these have been administered.

Reviewer's comments:

The testing algorithm was reviewed.

(b)(4)

Proposed Indications for Use

Cantab Mobile is intended to be used to assess memory in patients aged 50 to 90 years.

The application is designed to detect episodic memory impairments in patients aged 50 to 90 years who may be experiencing MCI or dementia (Table 1). Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression (Geriatric Depression Screening Questionnaire [GDS]), and problems with performing regular activities of daily living (Activities of Daily Life Questionnaire [ADL]). Additional

*information on questionnaires is provided in the Device Description document, **Section 11** of this submission.*

Indended Use (page 16)
Cantab Mobile's level of concern is classified as minor based upon the parameters and recommendations outlined in FDA's *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (2005), with negative responses to all questions in Tables 1 and 2. Regarding question 3 in Table 2, the app is a screening device for use by a learned intermediary in conjunction with other investigations; its operation does not lead directly to diagnosis or choice of appropriate medical care.

The predicate IFU is:
Cantab Mobile is substantially equivalent to DANA (manufactured by AnthroTronix; K141865).

Other predicate device: QbTest, Qbtech AB (K122149)

Table 3. Device Comparison Summary (Proposed Device vs. Predicate Device)

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	DANA – AnthroTronix (Submitted September 18, 2014)
510(k) Number	Not Yet Assigned	K141865
Trade Name	Cantab Mobile	DANA
Common Name:	Mobile Based Task Performance Recorder	
Classification Name:	Recorder, Attention Task Performance	
Regulatory Class:	Unclassified	
Indications for Use	Cantab Mobile is intended to be used to assess memory in patients aged 50 to 90 years. Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living.	DANA provides clinicians with objective measurements of reaction time (speed and accuracy) to aid in the assessment of an individual's medical or psychological state. DANA also delivers and scores standardized psychological questionnaires.

Reviewer's comments:

(b)(4)

(b)(4)

Clinical Performance Testing

(b)(4)

Inclusion Criteria: Not provided
Exlcusion Criteria: Not Provided

Reviewer's comments:

(b)(4)

Methods

Reviewer's comments:

(b)(4)

RISKS

(b)(4)

(b)(4)

SUMMARY

The submission raises concern of NSE based on the information provided (please see item #6 below). This and other points to be addressed are listed below:

1. (b)(4)
2. (b)(4)
3. (b)(4)
4. (b)(4)
5. (b)(4)
6. (b)(4)

(b)(4)

7. (b)(4)

Reviewer Sign-Off:	Christian N. Shenouda -S (Affiliate) Digitally signed by Christian N. Shenouda -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=2000945946, cn=Christian N. Shenouda -S (Affiliate) Date: 2016.07.07 14:14:37 -04'00'

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
CDRH/ODE/DNPMD/NSDB
WO66 RM2622
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
301-796-6475

Premarket Notification 510(k) Review

Date: July 8, 2016

Reviewer: Binoy Mathews

Subject: Traditional 510(k)# K161328

Applicant: Cambridge Cognition Ltd., Us Agent: Clementi Associates Ltd.	**Device Trade Name:** Cantab Mobile
Contact Name: Nancy Clementi	**Contact Title:** Chief Medical Officer, Clementi Associates Ltd.
Correspondent Firm: Clementi Associates Ltd	**Phone:** (610) 527-2600 **Email:** nancy.clementi@clempharma.net
Received Date: May 12, 2016	**Due Date:** August 10, 2016
Pro Code(s): LQD **Class:** Unclassified **Reg #:**	**Reg Name:**

Predicate Devices:

Submission #	Pro Code	Device Trade Name	Owner
K141865	LQD	Dana	Anthrotronix, Inc

Review Summary

Recommendation

I recommend that the Cantab Mobile is/are in need of Additional Information (AINN)

Review Team

Lead Reviewer	Binoy Mathews (CDRH/ODE/DNPMD/NSDB)
Clinical Reviewer	Christian Schenouda ,MD

I. Purpose and History

TPLC Information Recall Information Historyfalls

II. 510(k) Summary/Statement

510(k) Summary/Statement		
Was a 510(k) Summary or Statement provided?	Undo	Statement
The 510(k) Statement was prepared according to 21 CFR 807.93.		

Reviewer Recommendation
The 510(k) Statement is acceptable.

III. Device/System Description

Device Characteristics		Inadequate Or Marked
Is the intended use or fundamental technology new?	No	☐
Is the device life-supporting or life sustaining?	No	☐
Are there any direct or indirect patient contacting components?	No	☐
Does the device use software/firmware?	Yes	☐
• Is the device, or does it contain, a Mobile Medical App?	No	☐
Does the device or a component need sterilization (by manufacturer or user)?	No	☐
The device/system uses or is…	a reusable multi-patient use device(s)	☐
The environment for use of the device/system includes…	Home, Hospital	☐
Is the device a combination product?	N - Not a Part 3 Combination Product	☐
Is the device/system electrical (battery or wall powered)?	Yes, it is battery and mains powered	☐

Check the attributes that are applicable to this submission.

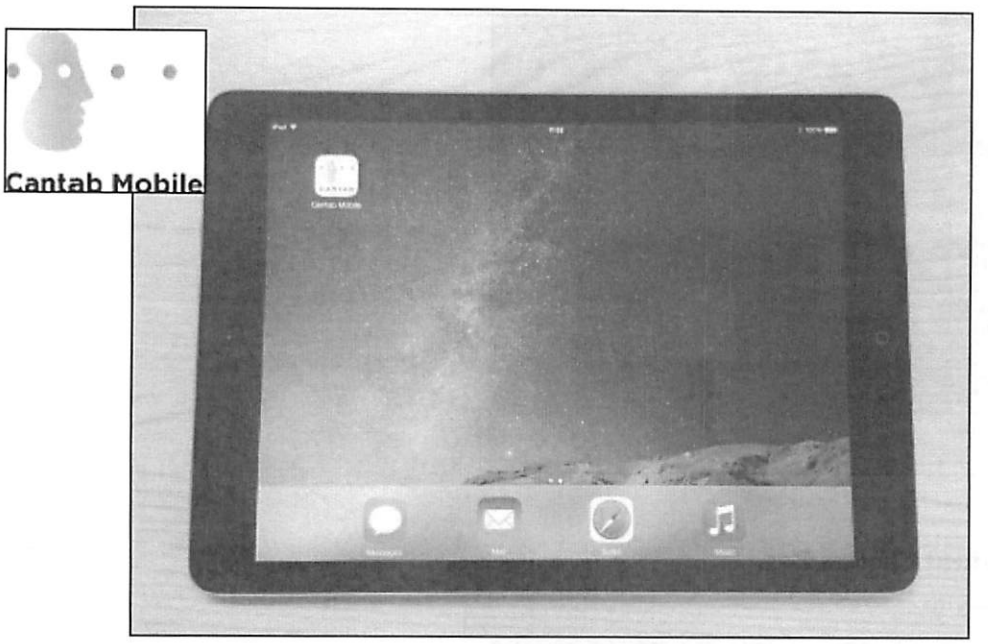
	Nanotechnology	Reprocessed SUD	Companion Diagnostic	Medical Counter Measures
Yes	☐	☐	☒	☐
No	☒	☒	☐	☒
Unknown	☐	☐	☐	☐

Device Description Table: Summary of important device characteristics

The Cantab Mobile is software which is loaded and run on Apple iPad. The software is intended to be administered by a healthcare professional to test the cognitive function of a patient. The Cantab Mobile memory test is based on the Cantab PAL test, which requires patients to learn and remember abstract visual patterns associated with various

locations on a touch sensitive computer screen. The Software also contains two additional (optional) questionnaires to assess a patient's mood and ability to perform daily living activities. At the end of the test, the software generates a report which summarizes the memory test results and also displays responses to the questionnaires.

Figure 1. iPad with App Icon at Top Left



The basic components of the device are the same as those of a standard iPad. Some of these are:

- The iPad
- iPad sleeve
- iPad stand
- iPad battery charger.

No prior calibration of this device is needed. Maintenance is limited to updating the software when new releases are made available and charging the device when needed. Support from the manufacturer will be required and periodic updates will be necessary.

The Cantab Mobile is indicated as an adjunct to assess memory in adults age 50 – 90. Specifically the subject device will assess visuospatial memory via usage of the Cantab PAL test. The Cantab PAL requires patients to learn and remember abstract visual patterns associated with various locations on an iPad. Patterns are presented in six boxes around the edge of the screen and the patient is required to touch the box in which they previously saw the pattern appear. If the locations are not recalled correctly, this is identified to the patient via audio prompts and pattern presentation and recall is repeated. The process continues until the task is completed. At this point, the next task is started. The whole test consists of a series of such tasks with increasing levels of difficulty. The patients responses are recoreded by screen touches. The number of errors are recorded and their performance is graded using algorithms derived from a normative database of around 4000 individuals collected during academic research in the UK, taking in account their age, gender, and level of education.

Memory Tests

The memory test is based on the Cantab PAL test and requires patients to learn and remember abstract visual pattersns associated with various locations on a touch sensitive computer screen. The patterns were all created to be bold, brightly colored, abstract with no cultural context.

Patterns are presented in six boxes around the edge of the screen. The patterns disapprea from the screen, leaving empty boxes and after a brief delay the same patterns are presented sequentially in the middle of the screen and the patient is required to touch the box in which they previously saw that pattern appear.

Figure 3. Pattern Appears in Box

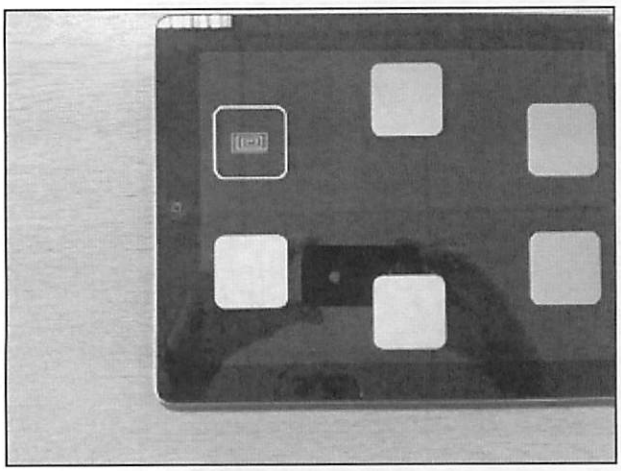
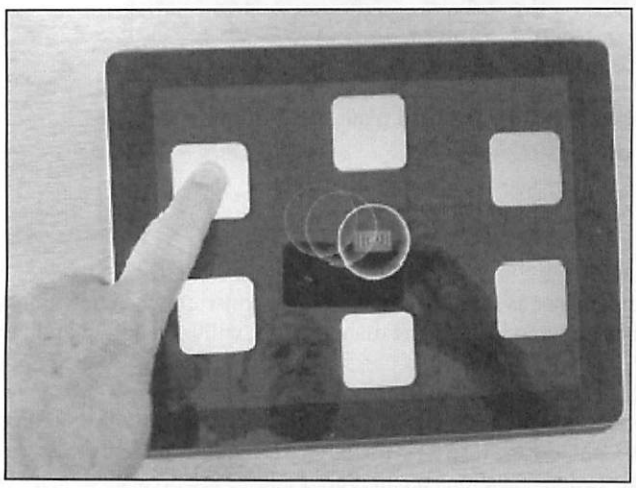


Figure 4. Patient Chooses Box



Clinical studies have demonstrated that the Cantab PAL measures of visuospatial associative learning and semantic memory are sensitive in detecting the earliest signs of prodromal Alzheimer's disease both in memory clinic attendees and in community dwelling cohorts of individuals classified as asymptomatic using current clinical measures.

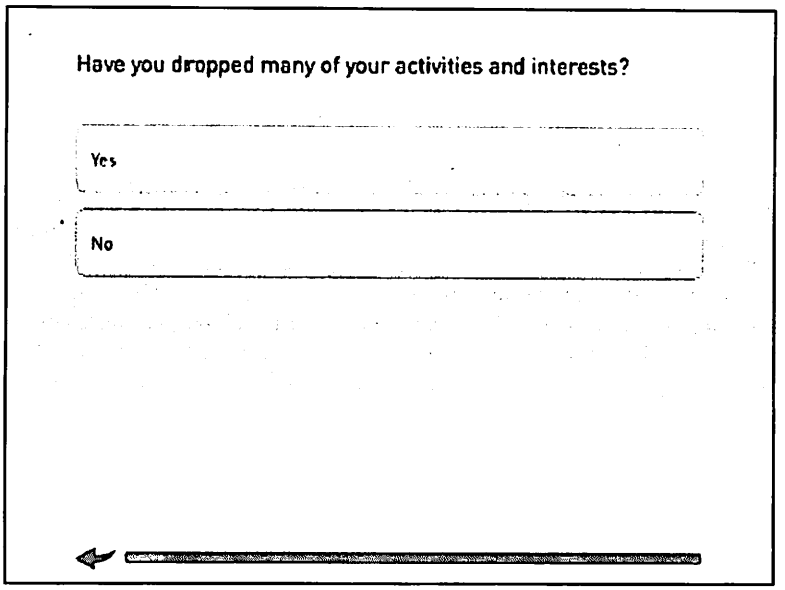
Cantab Mobile additionally includes optional questionaires. These include:

- GDS – Geriatric Depression Screening Questionaire
- ADL – Activities for Daily Living Questionaire

These questionnaires will be used to compare self-assessed memory to that compared to the normative database. Questionnaires operate by presenting a series of questions to the patient with clearly labeled response boxes that the

patient may touch in order to answer each question. The GDS rating scale in the app is the shorter version of GDS described by Yesavage et al, 1983 and comprises a series of questions each presented in turn textually on the screen using the language in force, two buttons to allow the patient to respond "yes" or "no" and a progress bar to give an approximate indication of progress.

Figure 5. GDS Rating Scale and Format



The ADL rating scale comprises a series of questions, earch presented in turn textually on the screen using the language in force, with introductory text given above the question and buttons below to allow the patients to choose from the responses permitted for the question. A progress bar is also present which gives an approximate indication of progress.

Results from the Cantab Mobile will be presented through the Report Manager. The following categories are reported:

1. Investigate or Red:
   This means that patient performance may indicate a clinically significant memory impairment (MCI or dementia). A red score is attained if
   - Test score was more than 1.5 standard deviations below the mean for people of their age, sex, and educational level.
   - Made more than 20 errors in the 6 pattern stage
   - Made several errors in the easier stages of the test.

2. Monitor or amber:
   This means that the patient's memory is in the lower end of the normal range. The patient may benefit from additional assessment or monitoring over time. An amber score is attained when:
   - A patient receives a score between 1 and 1.5 standard deviations below the expected level from someone of their age, sex, and educational level.

3. No Present Concern or Green:
   This means that the patient's memory appears normal at present. A green score is attained if:
   - They score no more than one standard deviation below the expected level for someone of their age, sex, and educational level.

Reviewer Comments:

The sponsor seeks to implement the Cantab PAL test on a mobile device as an adjunct test when assessing a patients memory. From an engineering perspective, the device description does not raise specific concerns. Dr. Christian Schenouda performed the clinical review for this device and provides the following comments regarding the device description:

- (b)(4)
- (b)(4)
- (b)(4)

For a table of device characteristics, see "Comparison of Technology to Predicate Devices" below.

Third-party Components and Accessories:

Reviewer Recommendation

The Device Description is not acceptable. The sponsor will need to address concerns stated above.

IV. Comparison of Indications for Use to Predicate Devices

Comparison of Indications for Use

Subject

510(k) #: K161328 Rx/OTC: Rx

Intended Population	Adults Only	Adults and Pediatrics	Transitional Adolescent A	Transitional Adolescent B	Adolescent	Child	Infant	Neonate/ Newborn
Yes	☒	☐	☐	☐	☐	☐	☐	☐
No	☐	☒	☒	☒	☒	☒	☒	☒
Unknown	☐	☐	☐	☐	☐	☐	☐	☐

Indications for Use: Cantab Mobile is intended to be used to assess memory in patients aged 50 to 90 years.

Predicate(s)

Submission#: K141865 Rx/OTC: Rx

Intended Population:

Indications for Use: DANA provides clinicians with objective measurements of reaction time (speed and accuracy) to aid in the assessment of an individual's medical or psychological state. Factors may affect the measurement of reaction time include, but are not limited to concussion, head injury, insomnia, post-traumatic stress disorder (PTSD), depression, attention deficit hyperactivity disorder (ADHD), memory impairment, dementia, delirium, prescription and non-prescription medication, some nutritional supplements, as well as a variety of psychological states (e.g. fatigue and stress)

Comparison of Indications for Use
DANA also delivers and scores standardized psychological questionnaires. DANA results should be interpreted only by qualified professionals.
Indications for Use Table: Compares the indications for use of the subject and predicate devices.

The subject device includes the following additional statement within the IFU comparison provided within Table 3 – Device Comparison Summary:

Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living.

Reviewer Comment:

(b)(4)

The sponsor may wish to consider the following devices as potential predicates:

- **DEN130033 – CogniView**
- **K150154 – ANAM**

(b)(4)

Per Dr. Shenoudah's clinical review memo:

- (b)(4)
- (b)(4)
- (b)(4)

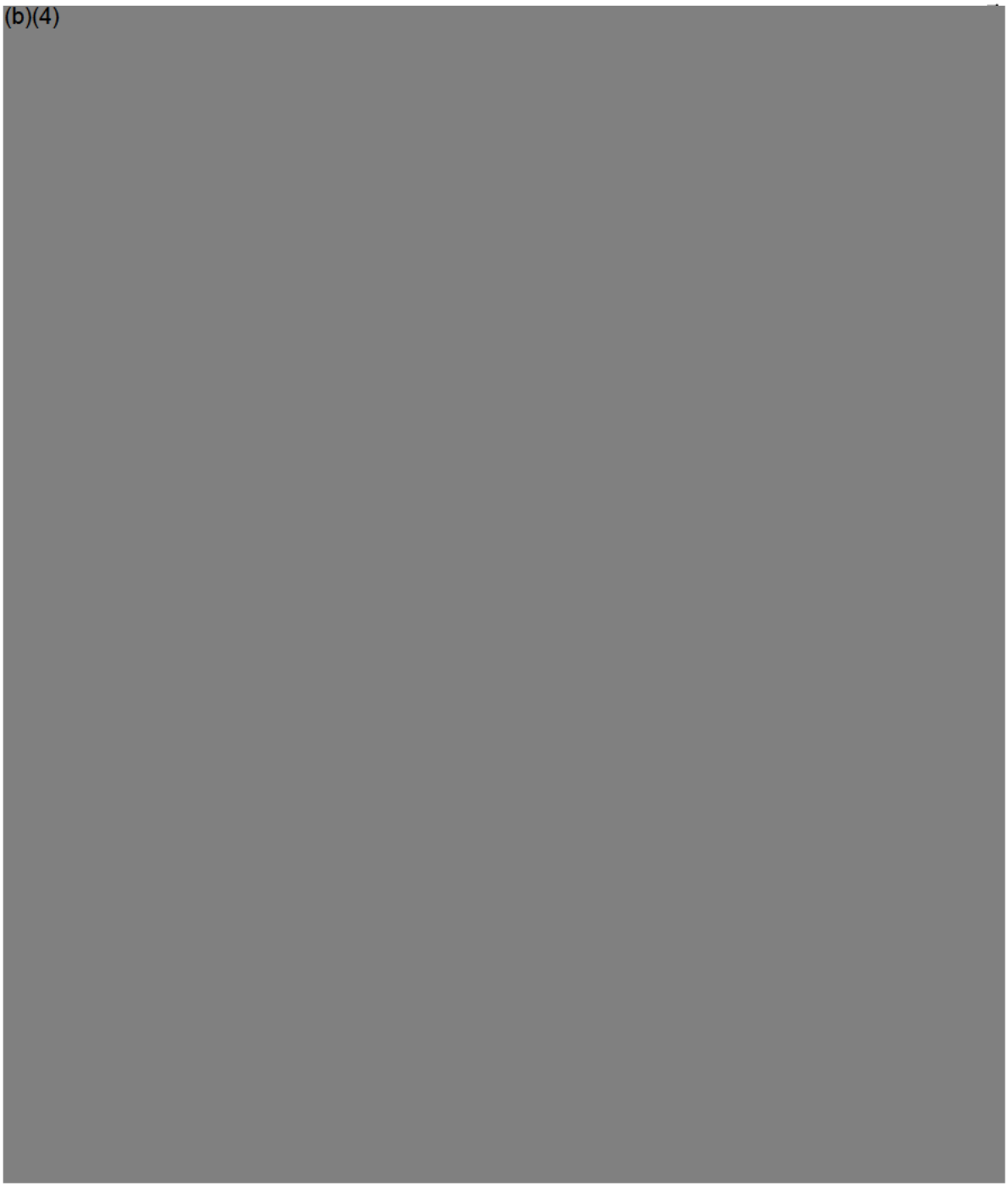
Reviewer Recommendation

The Comparison of the Indications for Use is not acceptable. (b)(4)

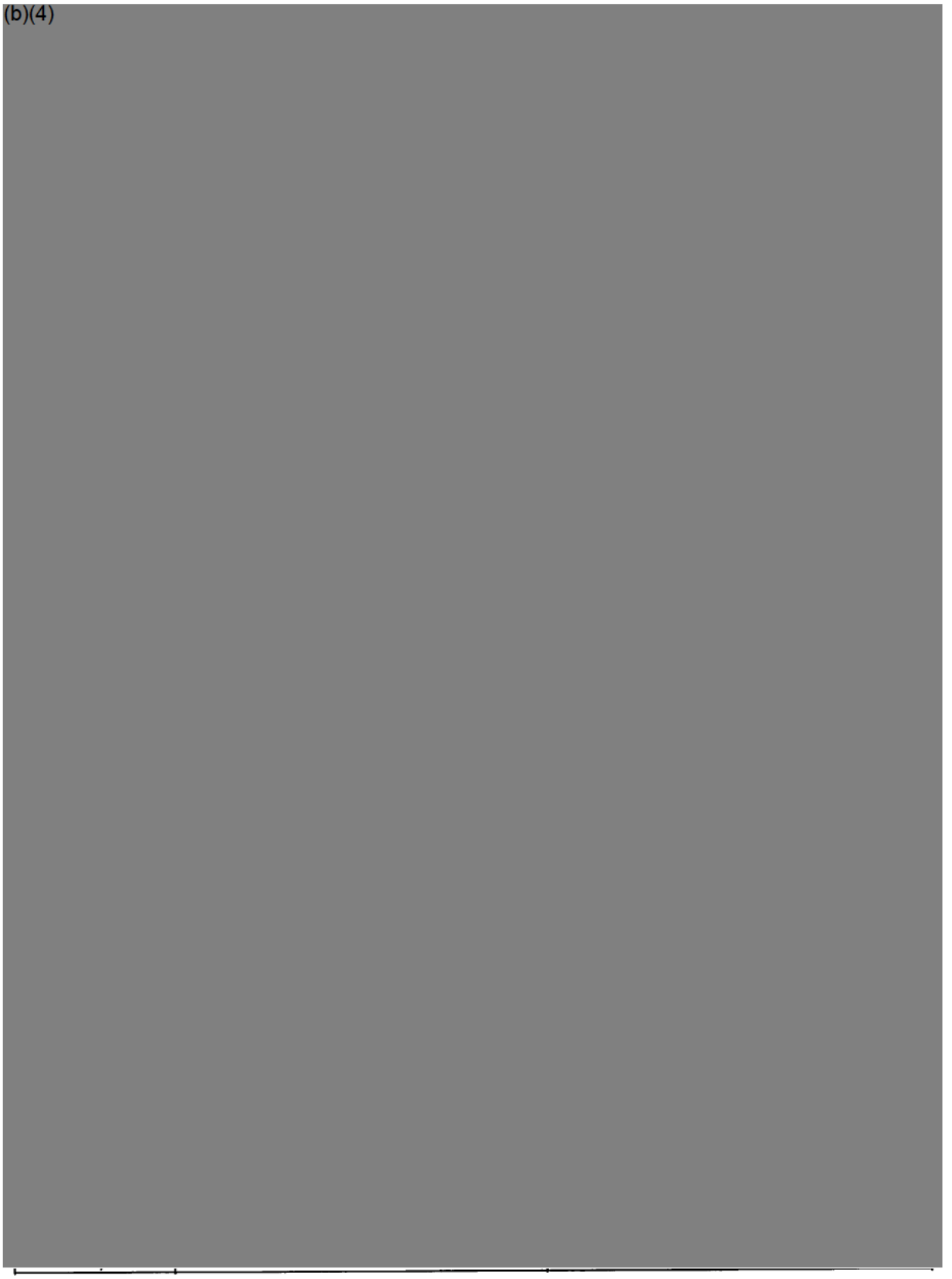
(b)(4)

V. Comparison of Technology to Predicate Devices

(b)(4)



(b)(4)



(b)(4)

Reviewer Comments:

(b)(4)

Reviewer Recommendation

The Comparison of the Technology to Predicate Devices is not acceptable since the choice of predicate is not appropriate.

VI. Labeling

Labeling Review Needed?	Yes	Undo
Usability Consult Needed?	Undo	No

Reviewer Comment: Labeling will be reviewed in greater detail once the sponsor provides an appropriate predicate device for comparison. Certain labeling changes have been suggested based on claims made within the labeling.

A General Labeling Requirements

General Labeling Requirements		Inadequate or Marked
Is the prescription statement (or "Rx only") included?	Yes	☐
The indications for use are consistent with the IFU page?	No	☒

Appropriate contraindications, warnings, precautions and adverse events provided?	No	☒
Instructions are in accordance with the guidance (if applicable)?	Inapplicable	☐
Appropriate labeling inside device?	Inapplicable	☐
Appropriate label/indicator outside device?	Inapplicable	☐
Appropriate Manual labeling?	No	☒
Is appropriate home use information included in the labeling?	Inapplicable	☐
What MRI safety information does the labeling contain?	MR Unsafe	☐

Labeling Table: A summary of the adequacy of several labeling requirements.

Reviewer Recommendation
The provided labeling is not appropriate and may need to be revised after selection of an appropriate predicate device. In addition, a number of other concerns have been raised with regard to language used within the labeling which will need to be revised.

VII. Reprocessing, Sterilization, and Shelf-Life

Reviewer Recommendation
Cleaning, Sterilization, Shelf-Life and Reuse descriptions are not applicable to this Device since it is software which runs on the Apple iPad tablet that is commercially available.

VIII. Biocompatibility

Reviewer Recommendation
Biocompatibility is not applicable to this device since it is software which runs on a commercially available tablet computer.

IX. Software/Firmware

Software Review Needed?	**Yes**	Undo
Software Consult Needed?	Undo	**No**

Software Documentation	Present	Absent	Inadequate
Software/Firmware Version: 1.3			
Level of Concern (LOC): Identified as Minor			☐
Software/Firmware description:	☐	☒	☒

Software Documentation	Present	Absent	Inadequate
Device Hazard Analysis:	☐	☒	☒
Software Requirements Specifications:	☐	☒	☒
Traceability Analysis/Matrix:	☐	☒	☒
Verification & Validation Testing: **Adequacy Comments:** Inadequate - Testing reports were not provided.	☒	☐	☐
Revision level history:	☐	☒	☒

Software Table: Demonstrates the adequacy of the software documentation according to the Guidance Document.

Reviewer Comment: The sponsor has appropriately designated the Software Level of Concern as Minor.
(b)(4)

(b)(4) **The sponsor will be requested to provide all sections which have been labelled inadequate above.**

Reviewer Recommendation
The Software is not acceptable.

X. EMC & Electrical, Mechanical and Thermal Safety & Risk Analysis

EMC Review Needed?	Undo	**No**
EMC Consult Needed?	Undo	**No**

Reviewer Recommendation
The software is run off of an Apple iPad. Therefore, EMC and EMT are not needed. The sponsor will be requested to provide a Risk Analysis to support the safety of the device.

XI. Performance Testing

A Bench Testing
None Provided

Reviewer Comment: The subject device is software which runs on the commercially available Apple iPad. Performance testing will be limited to the Software Verification and Validation testing and will be reviewed within the Software Section of this memo.

B Animal Testing
None Provided

C Clinical Testing

The following evidence was provided to support the clinical utility of the PAL:

- Case-control studies reported in published or unpublished meta analysis
- Narrative review of additional papers to support the performance of the tests.

(b)(4)

(b)(4)

Reviewer Recommendation

The Clinical Performance Testing is not acceptable.

XII. Kit Certification

This section is not usually needed. See the help text by clicking the heading.

XIII. Manufacturing Information

This section is not usually needed. See the help text by clicking the heading.

XIV. References

XV. SE Flowchart Questions

Substantial Equivalence Determination	Yes	No
Is the predicate device legally marketed?	☒	☐
Do the devices have the same intended use?	☐	☒

Please explain how the intended use of the subject device is similar to or different from the predicate device:
The subject device is indicated to assess memory while the chosen predicate was cleared to assess reaction time. Memory and Reaction Time are two different cognitive processes and therefore are not equivalent.

XVI. Original Deficiencies

Administrative Information

1. (b)(4) [redacted]

2. (b)(4) [redacted]

Device Description

3. (b)(4) [redacted]

4. (b)(4) [redacted]

5. (b)(4)

Labeling

6. (b)(4)

7. (b)(4)

Software

8. (b)(4)

a. (b)(4)

b. (b)(4)

c. (b)(4)

d. (b)(4)

e. (b)(4)

f. (b)(4)

These documents are necessary to ensure the safety and effectiveness of the device through adequate design and documentation. Please provide these documents.

Performance Testing

9. (b)(4)

XVII. Contact History

Digital Signature Concurrence Table	
Reviewer Sign-Off	Binoy J. Mathews -S 2016.07.08 13:07:45 -04'00'

FOOD AND DRUG ADMINISTRATION MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
White Oak, MD 20993

510(k) MEMORANDUM
Medical Officer Review

Date: January 9rd, 2017
To: Binoy Mathews, PhD.
From: Christian Shenouda, MD - DNPMD

Device Name: CANTAB Mobile
Sponsor: Cambridge Cognition Limited

RECOMMENDATION: SE

The sponsor has submitted a 510k for approval of the CANTAB Mobile device to assess visuospatial memory in adults aged 50 to 90 years of age. In the most recently submitted supplement, the sponsor has presented responses to concerns and deficiencies identified by FDA. I have reviewed the responses as well as the supporting material. Via interactive communication with FDA the sponsor has provided adequate responses and the product appears to be substantially equivalent to the identified predicate.

SUMMARY

This is a consult for a clinical review of a 510(k) submission K161328_S001 for the CANTAB Mobile device. The device is used to assess visuospatial memory in adults aged 50 to 90 years of age. The sponsor previously provided literature to support the examination of the visuospatial cognitive domain as an early indicator of cognitive decline. The device is indicated for clinician use to help identify individuals with early cognitive impairments and does not replace a clinical examination. The testing is administered via an iPad which has a computerized version of the CANTAB PAL test. The sponsor has also included tests for mood disturbance and ADL function. Results are provided for clinician interpretation and the user interface has been modified based on previous FDA comments.

I have reviewed the sponsor's responses and find them adequate to address the identified concerns. Additionally, I do not believe that usage as described poses danger to the public and therefore recommend that the mission of SE for this product.

REVIEW

Device Description

Cantab Mobile is software to be loaded and run on Apple iPad hardware and operating system (Figure 1). Below is a list of possible device accessories:

- *The iPad1 is an essential accessory*
- *Disposable iPad Sleeve (see also **Instructions for Use**) for cleaning recommendations)*
- *iPad stand*
- *A iPad battery charger is also supplied with the iPad*

Memory Test

(b)(4)

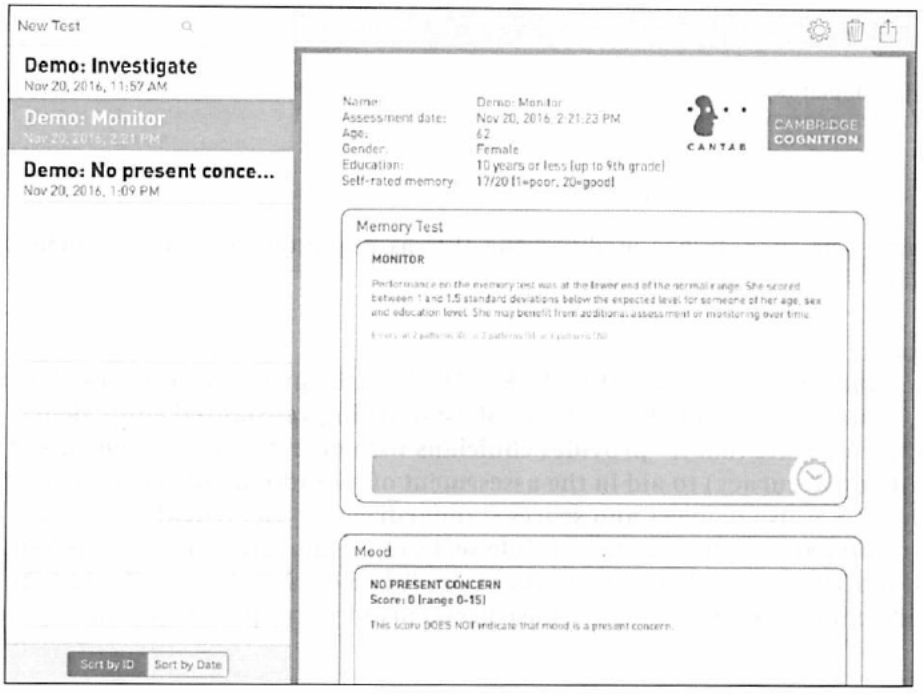
Other Tests

Cantab Mobile additionally includes optional questionnaires.

1.GDS – Geriatric Depression Screening Questionnaire (See Appendix C)
2.ADL – Activities for Daily Living Questionnaire (See Appendix D)

Reporting

Figure 6. Report Manager



(b)(4)

Proposed Indications for Use

The device is intended to be used to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years.

Contraindications

Patients with severe visual impairment
Patients outside the indicated age range

The predicate IFU is:

Reviewer's comments: The sponsor has modified the IFU as requested (see item #2 below). No additional information is requested at this time.

1. **FDA Comment:**

(b)(4)

(b)(4)

Sponsor Response:

(b)(4)

5.1 Predicate Device

Cantab Mobile is substantially equivalent to Cognivue (manufactured by Cerebral Assessment Systems; DEN130033). Cantab Mobile and Cognivue are both categorized as Computerized

Cognitive Assessment Aids. The tests use different devices; Cantab Mobile uses an Apple iPad and Cognivue uses a personal computer on a cart. Cantab Mobile and Cognivue are both used by healthcare professionals to measure aspects of patients' cognition. Cantab Mobile and Cognivue differ in the areas of cognition measured in that Cantab Mobile specifically assesses memory using a test of visuospatial associative learning (PAL) that is known to be correlated with hippocampal function, whereas the Cognivue software gives an overview of brain health, including memory, using ten short tests.
Cognivue is designed to be used to regularly monitor a patient's broad cognitive health, using 10 short tests to indicate decline, and potentially dementia, through comparison to baseline test performance of other age-normal adults.
Cantab Mobile and Cognivue are similar in terms of technological characteristics as both electronically record objective performance measurements when the patient responds to stimuli presented on the screen. Differences in the design and performance of Cantab Mobile and Cognivue do not affect either the safety or effectiveness of Cantab Mobile for its intended use.

Table 2. Device Comparison Summary (Proposed Device vs. Predicate Device)

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	Cognivue – Cerebral Assessment Systems, Inc. (Submitted June 26, 2013)
510(k) Number	K161328	DEN130033
Trade Name	Cantab Mobile	Cognivue
Regulation Name:	Computerized Cognitive Assessment Aid	
Intended Use	Cantab Mobile is intended to be used to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years. Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living. Results should be interpreted only by qualified professionals. The device is not intended to be used as a stand-alone diagnostic device. The device is not intended to identify the presence or absence of clinical diagnoses.	Cognivue testing is indicated as an adjunctive tool for evaluating perceptual and memory function in individuals aged 55 to 95 years old. Results should be interpreted only by qualified professionals. The device is not intended to be used as a stand-alone diagnostic device. The device is not intended to identify the presence or absence of clinical diagnoses.

FDA REVIEWER COMMENT: (b)(4)
(b)(4)

2. FDA Comment:

(b)(4)

Sponsor Response:

(b)(4)

FDA REVIEWER COMMENT: The revised IFU is noted and adequate. No further information is requested.

3. FDA Comment:

(b)(4)

Sponsor Response:

(b)(4)

(b)(4)

FDA REVIEWER COMMENT: (b)(4)

(b)(4)

(b)(4)

(b)(4) **No further information is needed.**

4. FDA Comment:

(b)(4)

(b)(4)

FDA 4a Comment:

(b)(4)

Sponsor 4a Response:

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

FDA 4b Comment:

(b)(4)

Sponsor 4b Response:

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

FDA 4c Comment:

(b)(4)

Sponsor 4c Response:

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

5. FDA Comment:

(b)(4)

Sponsor Response:

(b)(4)

FDA REVIEWER COMMENT: Additional information is needed. Although the sponsor has

(b)(4)

(b)(4)

6. FDA Comment:

(b)(4)

FDA 6a Comment:

"6a. (b)(4)
(b)(4)

Sponsor 6a Response:

(b)(4)

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

FDA 6b Comment:

"6b. (b)(4)
(b)(4)

Sponsor 6b Response:

(b)(4)

(b)(4)

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

FDA 6c Comment:
6c. (b)(4)
(b)(4)

Sponsor 6c Response:
Verification and Validation testing
(b)(4)

Additional information is provided in **Response to Deficiency Item 6c: Cantab Mobile Verification and Validation.**

Test-retest reliability
(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

SUMMARY

The sponsor has adequately addressed FDA concerns via this supplement and interactive communication with the lead reviewer. The device description, IFU, and user interface appear safe and effective for its stated usage. I support the SE designation of this device.

Reviewer Sign-Off:	Christian N. Shenouda -S (Affiliate) Digitally signed by Christian N. Shenouda -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=2000945946, cn=Christian N. Shenouda -S (Affiliate) Date: 2017.01.09 08:36:44 -05'00'

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
CDRH/ODE/DNPMD/NSDB
WO66 RM2622
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
301-796-6475

Premarket Notification 510(k) Review

Date: January 12, 2017

Reviewer: Binoy Mathews

Subject: Traditional 510(k)# K161328/S001

Applicant: Cambridge Cognition Ltd., Us Agent: Clementi Associates Ltd.	**Device Trade Name:** Cantab Mobile
Contact Name: Nancy Clementi	**Contact Title:** Chief Medical Officer, Clementi Associates Ltd.
Correspondent Firm: Clementi Associates Ltd	**Phone:** (610) 527-2600 **Email:** nancy.clementi@clempharma.net
Received Date: December 21, 2016	**Due Date:** January 16, 2017
Pro Code(s): PKQ **Class:** II **Reg #:** 882.1470	**Reg Name:** Computerized Cognitive Assessment Aid

Predicate Devices:

Submission #	Pro Code	Device Trade Name	Owner
DEN130033	PKQ	Cognivue	Cerebral Assessment Systems, Inc.

Review Summary

The subject device is a Computerized Cognitive Assessment Aid with the following Indications for Use: "The device is intended to be used to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years." It is for Rx use.

Recommendation

I recommend that the Cantab Mobile is/are Substantially Equivalent (SESE)

Review Team

Lead Reviewer	Binoy Mathews (ODE/DNPMD/NSDP)
Clinical Reviewer	Christian Shenouda ,MD (ODE/DNPMD)

I. Purpose and History

TPLC Information Recall Information Historyfalls

II. 510(k) Summary/Statement

510(k) Summary/Statement		
Was a 510(k) Summary or Statement provided?	Undo	Statement
The 510(k) Statement was prepared according to 21 CFR 807.93.		

Reviewer Recommendation
The 510(k) Statement is acceptable.

III. Device/System Description

Device Characteristics		Inadequate Or Marked
Is the intended use or fundamental technology new?	No	☐
Is the device life-supporting or life sustaining?	No	☐
Are there any direct or indirect patient contacting components?	No	☐
Does the device use software/firmware?	Yes	☐
• Is the device, or does it contain, a Mobile Medical App?	No	☐
Does the device or a component need sterilization (by manufacturer or user)?	No	☐
The device/system uses or is…	a reusable multi-patient use device(s)	☐
The environment for use of the device/system includes…	Home, Hospital	☐
Is the device a combination product?	N - Not a Part 3 Combination Product	☐
Is the device/system electrical (battery or wall powered)?	Yes, it is battery and mains powered	☐

Check the attributes that are applicable to this submission.

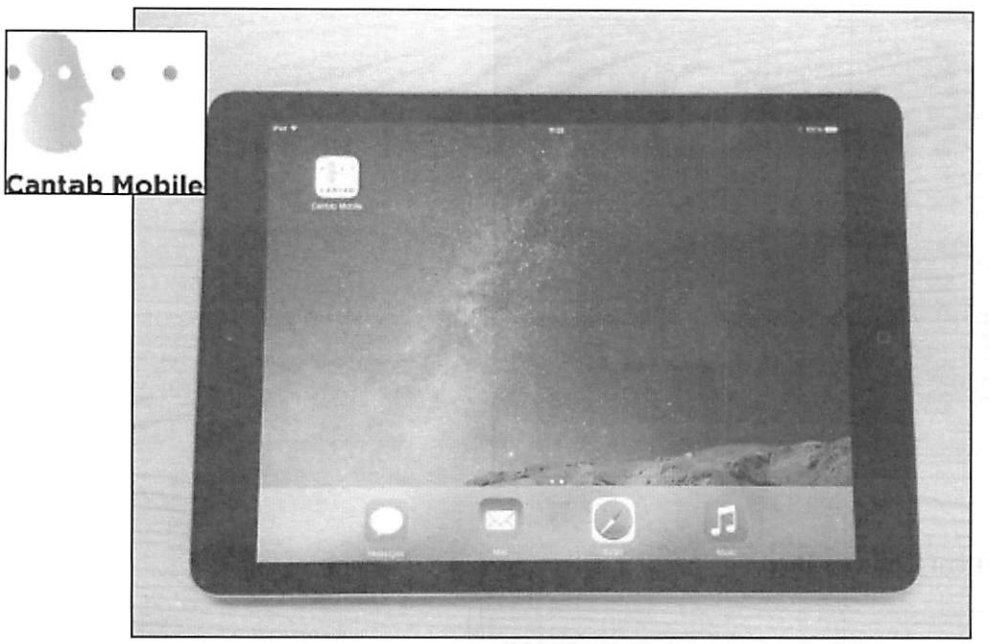
	Nanotechnology	Reprocessed SUD	Companion Diagnostic	Medical Counter Measures
Yes	☐	☐	☒	☐
No	☒	☒	☐	☒
Unknown	☐	☐	☐	☐

Device Description Table: Summary of important device characteristics

The Cantab Mobile is software which is loaded and run on Apple iPad. The software is intended to be administered by a healthcare professional to test the cognitive function of a patient. The Cantab Mobile memory test is based on the Cantab PAL test, which requires patients to learn and remember abstract visual patterns associated with various

locations on a touch sensitive computer screen. The Software also contains two additional (optional) questionnaires to assess a patient's mood and ability to perform daily living activities. At the end of the test, the software generates a report which summarizes the memory test results and also displays responses to the questionnaires.

Figure 1. iPad with App Icon at Top Left



The basic components of the device are the same as those of a standard iPad. Some of these are:

- The iPad
- iPad sleeve
- iPad stand
- iPad battery charger.

No prior calibration of this device is needed. Maintenance is limited to updating the software when new releases are made available and charging the device when needed. Support from the manufacturer will be required and periodic updates will be necessary.

The Cantab Mobile is indicated as an adjunct to assess memory in adults age 50 – 90. Specifically the subject device will assess visuospatial memory via usage of the Cantab PAL test. The Cantab PAL requires patients to learn and remember abstract visual patterns associated with various locations on an iPad. Patterns are presented in six boxes around the edge of the screen and the patient is required to touch the box in which they previously saw the pattern appear. If the locations are not recalled correctly, this is identified to the patient via audio prompts and pattern presentation and recall is repeated. The process continues until the task is completed. At this point, the next task is started. The whole test consists of a series of such tasks with increasing levels of difficulty. The patients responses are recoreded by screen touches. The number of errors are recorded and their performance is graded using algorithms derived from a normative database of around 4000 individuals collected during academic research in the UK, taking in account their age, gender, and level of education.

Memory Tests

The memory test is based on the Cantab PAL test and requires patients to learn and remember abstract visual pattersns associated with various locations on a touch sensitive computer screen. The patterns were all created to be bold, brightly colored, abstract with no cultural context.

Patterns are presented in six boxes around the edge of the screen. The patterns disapprea from the screen, leaving empty boxes and after a brief delay the same patterns are presented sequentially in the middle of the screen and the patient is required to touch the box in which they previously saw that pattern appear.

Figure 3. Pattern Appears in Box

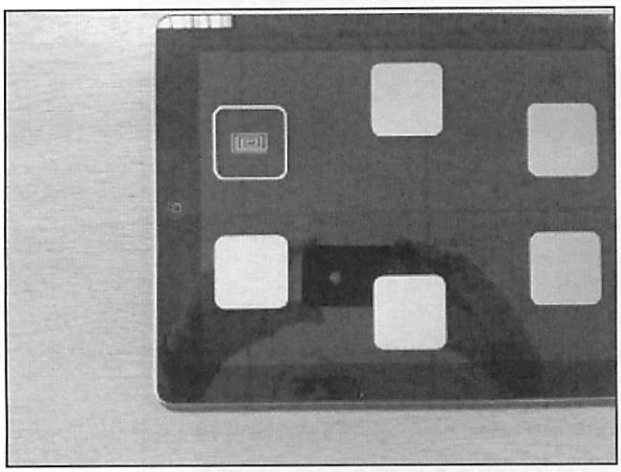
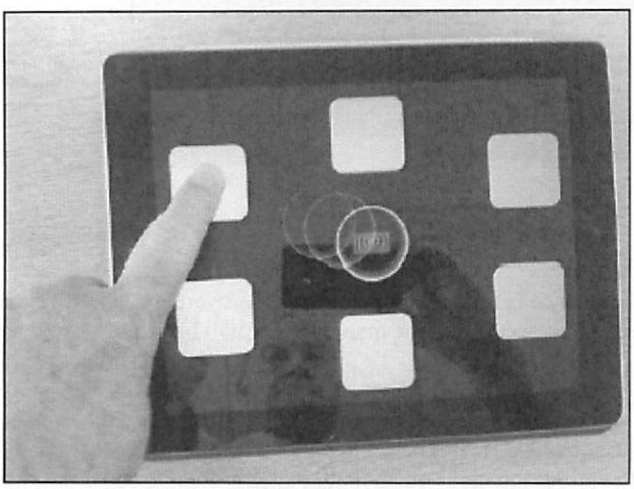


Figure 4. Patient Chooses Box



Clinical studies have demonstrated that the Cantab PAL measures of visuospatial associative learning and semantic memory are sensitive in detecting the earliest signs of prodromal Alzheimer's disease both in memory clinic attendees and in community dwelling cohorts of individuals classified as asymptomatic using current clinical measures.

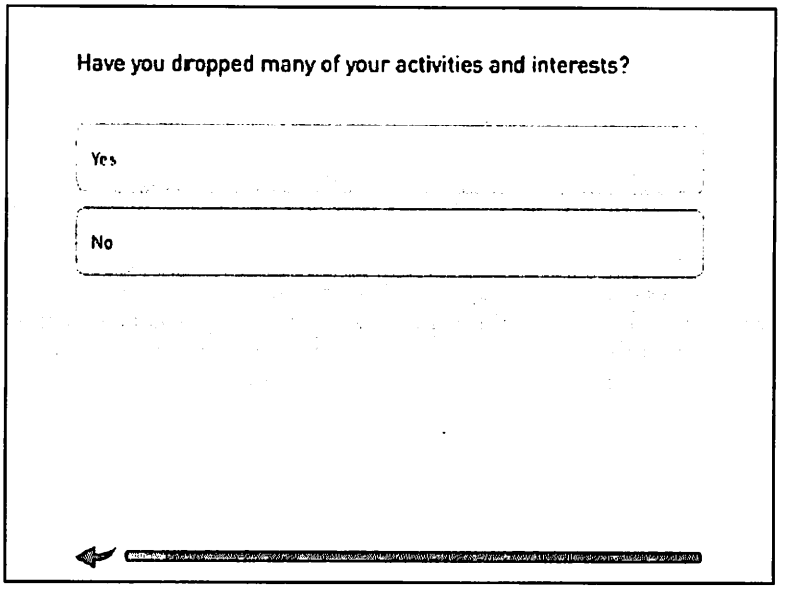
Cantab Mobile additionally includes optional questionaires. These include:

- GDS – Geriatric Depression Screening Questionaire
- ADL – Activities for Daily Living Questionaire

These questionnaires will be used to compare self-assessed memory to that compared to the normative database. Questionnaires operate by presenting a series of questions to the patient with clearly labeled response boxes that the

patient may touch in order to answer each question. The GDS rating scale in the app is the shorter version of GDS described by Yesavage et al, 1983 and comprises a series of questions each presented in turn textually on the screen using the language in force, two buttons to allow the patient to respond "yes" or "no" and a progress bar to give an approximate indication of progress.

Figure 5. GDS Rating Scale and Format



The ADL rating scale comprises a series of questions, earch presented in turn textually on the screen using the language in force, with introductory text given above the question and buttons below to allow the patients to choose from the responses permitted for the question. A progress bar is also present which gives an approximate indication of progress.

Results from the Cantab Mobile will be presented through the Report Manager. The following categories are reported:

1. Investigate or Red:
   This means that patient performance may indicate a clinically significant memory impairment (MCI or dementia). A red score is attained if
   - Test score was more than 1.5 standard deviations below the mean for people of their age, sex, and educational level.
   - Made more than 20 errors in the 6 pattern stage
   - Made several errors in the easier stages of the test.

2. Monitor or amber:
   This means that the patient's memory is in the lower end of the normal range. The patient may benefit from additional assessment or monitoring over time. An amber score is attained when:
   - A patient receives a score between 1 and 1.5 standard deviations below the expected level from someone of their age, sex, and educational level.

3. No Present Concern or Green:
   This means that the patient's memory appears normal at present. A green score is attained if:
   - They score no more than one standard deviation below the expected level for someone of their age, sex, and educational level.

Original Reviewer Comments:

The sponsor seeks to implement the Cantab PAL test on a mobile device as an adjunct test when assessing a patients memory. From an engineering perspective, the device description does not raise specific concerns. Dr. Christian Schenouda performed the clinical review for this device and provides the following comments regarding the device description:

- (b)(4)
- (b)(4)
- (b)(4)

S001 Reviewer Comments:

With respect to these concerns the following deficiencies were communicated to the sponsor:

1. (b)(4)

Sponsor's Response: Taken from Dr. Shenouda's Clinical Review:

(b)(4)

(b)(4)

FDA REVIEWER COMMENT: (b)(4)
(b)(4)

ADDENDUM 1/9/16 – The sponsor has communicated with FDA and removed the identified wording. No further information is needed.

2. (b)(4)

a. (b)(4)

Sponsor 4a Response:

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

Lead Reviewer Comment:

The sponsor has included additional information within their response addressing how results from the ADL and GDS will be presented to the physician. This information can be found within

K161328/S001 –Device Description Section 1.4.2 What is reported. The sponsor provides a detailed description of how the results from these two optional tests are presented within the Test Results.

b. (b)(4)

Sponsor 4b Response:
(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

Lead Reviewer Comment:
Clarification provided by the sponsor states that the version of the GDS being used is the GDS-15 which was validated by Almeida and Almeida 1999

The version of the ADL included in the App was developed and validated by Galasko et all 2006.

Lead Reviewer Comment:

c. (b)(4)

Sponsor 4c Response:
(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

3. (b)(4)

Sponsor Response:
(b)(4)

FDA REVIEWER COMMENT: (b)(4)
(b)(4)

ADDENDUM 1/9/16- The sponsor has provided confirmation that changes will be made to the software. The sponsor provided a revised Device Description. No further information is needed at this time.

For a table of device characteristics, see "Comparison of Technology to Predicate Devices" below.

Third-party Components and Accessories:

Reviewer Recommendation
The Device Description is acceptable.

IV. Comparison of Indications for Use to Predicate Devices

Comparison of Indications for Use

Subject

510(k) #: K161328 Rx/OTC: Rx

Intended Population	Adults Only	Adults and Pediatrics	Transitional Adolescent A	Transitional Adolescent B	Adolescent	Child	Infant	Neonate/ Newborn
Yes	☒	☐	☐	☐	☐	☐	☐	☐
No	☐	☒	☒	☒	☒	☒	☒	☒
Unknown	☐	☐	☐	☐	☐	☐	☐	☐

Indications for Use: The device is intended to be used as an adjunctive tool to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years.

Predicate(s)

Submission#: DEN130033 Rx/OTC: Rx

Intended Population:

Indications for Use: Cognivue testing is indicated as an adjunctive tool for evaluating perceptual and memory function in individuals aged 55-95 years old.

Indications for Use Table: Compares the indications for use of the subject and predicate devices.

The subject device includes the following additional statement within the IFU comparison provided within Table 3 – Device Comparison Summary:

Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living.

Original Reviewer Comment:

(b)(4)

The sponsor may wish to consider the following devices as potential predicates:

- **DEN130033 – CogniView**
- **K150154 – ANAM**

(b)(4)

Per Dr. Shenoudah's clinical review memo:

- (b)(4)
- (b)(4)
- (b)(4)

(b)(4)

S001 Reviewer Comment:

The following deficiency was communicated to the sponsor during the original review:

1. (b)(4)

Sponsor Response:

Per the Division's recommendation above, the Sponsor has updated the predicate device for comparison to Cognivue. The Executive Summary (Section 5.1 and Appendix A) as well as CDRH Premarket Review Submission Cover Sheet, FDA Form 3514 have been updated to reflect this change and are submitted herein.

Reviewer Comment:

The sponsor has changed their predicate to the Cognivue System. Dr. Shenouda and I both agree that the Cognivue is more suitable as a predicate for the Cantab Mobile device than the ANAM Test System.

Per Dr. Shenouda:

(b)(4)

(b)(4)

No further information is required.

Reviewer Recommendation

The Comparison of the Indications for Use is acceptable. The sponsor has chosen the Cognivue System as a new predicate.

V. Comparison of Technology to Predicate Devices

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	DANA - AnthroTronix
510(k) Number	Not Yet Assigned	K141865
Device Information: Trade Name	Cantab Mobile	DANA
Device Information: Common Name:	Mobile Based Task Performance Recorder	Mobile Based Task Performance Recorder
Device Information: Classification Name:	Recorder, Attention Task Performance	Recorder, Attention Task Performance
Device Information: Device Class:	Unclassified The device has the same intended use, indications for use, and relies on technology that does not raise new safety and effectiveness questions to DANA.	Unclassified http://www.accessdata.fda.gov/cdrh_docs/pdf14/k141814.pdf
Predicate Device:	DANA (K141865)	QbTest, Qbtech AB (K122149)
Type of Use	Prescription Use (Part 21 CRF 801 Subpart D	Prescription Use (Part 21 CFR 801 Subpart D)
Submission Date:	TBD	September 18, 2014
Submitter Information: Company:	Cambridge Cognition Limited. Tunbridge Court, Tunbridge Lane Bottisham Cambridgeshire, CB25 9TU UK	AnthroTronix, Inc. 8737 Colesville Road, Suite L203 Silver Spring, MD 20910 USA
Design and Intended Use	Cantab Mobile is a mobile application indicated to provide clinicians with objective measurements of visuospatial episodic memory and mood to aid in the assessment of an individual's medical or psychological state. Results should be interpreted only by qualified professionals. Cantab Mobile was developed on a mobile platform to improve the access and availability of assessments.	DANA is a mobile application indicated to provide clinicians with objective measurements of reaction time (speed and accuracy) and standardized health assessments to aid in the assessment of an individual's medical or psychological state. Results should be interpreted only by qualified professionals. DANA was developed on a mobile platform to improve the access and availability of assessments.

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	DANA - AnthroTronix
Target population	Patients aged 50 to 90 years with concerns about their memory. Results are automatically adjusted for age, gender, education.	A wide age range from high school students to older patients with dementia.
Anatomical site	The brain: cognitive function	The brain: cognitive function
Test duration	The test takes approximately 10 minutes to complete.	Spectrum of tests: 5-Minute Rapid; 15-Minute Brief; 45-Minute Standard.
Scoring and reports	Automatic scoring and instant reports	Automatic scoring and instant reports
Where used	Cantab Mobile is software used on a tablet, therefore it can be administered in any suitable setting, e.g. a clinic or home.	DANA is software on a tablet or smartphone, therefore it can be administered anywhere.
Energy used	Cantab Mobile software runs on an Apple iPad, which has the following features: ▪ built-in 25-watt-hour rechargeable lithium-polymer battery; ▪ charging via power adapter or USB to computer system; ▪ up to 10 hours of use when charged.	The DANA software runs on Android tablets and smartphones, containing a rechargeable battery, charged via power adapter or USB to computer system. The energy used is hardware-dependent.
Human factors	Any healthcare professional can administer the test. To ensure reliable results, the iPad should be placed on a stand and the assessment should be administered in a quiet room, without disturbance. The voiceover and questionnaire texts are provided in a choice of languages.	DANA software can be self-administered by patients or administered by a health aide.
To whom is the product marketed /target audience?	Healthcare Rehabilitation	Healthcare Education Pharmaceutical Rehabilitation Government
Materials	N/A	N/A
Biocompatibility	N/A	N/A
Compatibility with the environment and other devices	N/A	N/A
Sterility	Sterility status is not needed for this software-only device	Sterility status is not needed for this software-only device
Safety: electrical; mechanical; chemical;	These safety issues are not applicable to this software-only device.	These safety issues are not applicable to this software-only device.

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	DANA - AnthroTronix
thermal; radiation.		
To whom is the product marketed /target audience?	Healthcare Rehabilitation	Healthcare Education Pharmaceutical Rehabilitation Government
How the device differs from Predicate device	Cantab Mobile is similar to DANA in terms of technological characteristics, as both electronically record objective performance accuracy as the patient responds to stimuli presented on the screen by touching the screen. Cantab Mobile differs from DANA in that it provides an assessment of episodic memory, compared to DANA which assesses attention. Cantab Mobile also presents assessments of depression and activities of daily living, which are not included in DANA.	

Original Reviewer Comments:

(b)(4)

S001 Reviewer Comment:

The sponsor has revised their Device Comparison Table to reflect their new primary predicate, Cognivue.

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	Cognivue – Cerebral Assessment Systems, Inc.
510(k) Number	K161328	DEN130033
Device Information: Trade Name	Cantab Mobile	Cognivue
Regulation Name:	Computerized Cognitive Assessment Aid Classification Regulation # CFR 882.1470	Computerized Cognitive Assessment Aid Classification Regulation # CFR 882.1470
Product Code	PKQ	PKQ
Device Information: Device Class:	Unclassified or Proposed Class I The device has the same intended use, and relies on technology that does not raise new safety and effectiveness questions to Cognivue.	Class II
Predicate Device:	Cognivue (DEN130033)	*De novo* submission
Type of Use	Prescription Use (Part 21 CFR 801.109)	Prescription Use (Part 21 CFR 801.109)
Submission Date:	May 12, 2016	June 26, 2013
Submitter Information: Company:	Cambridge Cognition Limited Tunbridge Court, Tunbridge Lane Bottisham Cambridgeshire, CB25 9TU UK	Cerebral Assessment Systems, Inc. 2850 Clover Street Pittsford, NY 14534 USA
Design and Intended Use	Cantab Mobile is intended to be used to assess memory by testing visuospatial associative learning in patients aged 50 to 90 years. Along with the memory test there are optional mood and functional assessments which can help detect symptoms of depression, and problems with performing regular activities of daily living. Results should be interpreted only by qualified professionals. The device is not intended to be used as a stand-alone diagnostic device. The device is not intended to identify the presence or absence of clinical diagnoses.	Cognivue testing is indicated as an adjunctive tool for evaluating perceptual and memory function in individuals aged 55 to 95 years old. Results should be interpreted only by qualified professionals. The device is not intended to be used as a stand-alone diagnostic device. The device is not intended to identify the presence or absence of clinical diagnoses.

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	Cognivue – Cerebral Assessment Systems, Inc.
Target population	Patients aged 50 to 90 years with concerns about their memory. Results are automatically adjusted for age, gender, education.	Patients aged 55 to 95 years for the purpose of identifying a potential decline in cognitive function relative to baseline test performance of other age-normal adults.
Anatomical site	The brain: cognitive function	The brain: cognitive function
Test duration	The test takes approximately 10 minutes to complete.	The test takes approximately 10 minutes to complete.
Scoring and reports	Automatic scoring and instant reports	Automatic scoring and instant reports
Where used	Cantab Mobile is software used on a tablet, therefore it can be administered in any suitable setting, e.g. a clinic or home.	The Cognivue software is used on a personal computer, situated on a cart to provide mobility within the healthcare setting.
Energy used	Cantab Mobile software runs on an Apple iPad, which has the following features: • built-in 25-watt-hour rechargeable lithium-polymer battery; • charging via power adapter or USB to computer system; • up to 10 hours of use when charged.	The Cognivue software runs on a personal computer – the energy used is hardware-dependent.
Human factors	Any healthcare professional can administer the test. To ensure reliable results, the iPad should be placed on a stand and the assessment should be administered in a quiet room, without disturbance. The voiceover and questionnaire texts are provided in a choice of languages.	Any healthcare professional can administer the test. The battery is organized into three sub-batteries, with each sub-test preceded by transitional guidance that facilitates the test subject's engagement with minimal supervision.
To whom is the product marketed /target audience?	Healthcare Rehabilitation	Healthcare
Materials	N/A	N/A
Biocompatibility	N/A	N/A
Compatibility with the environment and other devices	N/A	N/A
Sterility	Based on the device function there is no sterilization testing required for this device.	Based on the device function there is no sterilization testing required for this device.

Comparison Items	CANTAB Mobile- Cambridge Cognition Ltd.	Cognivue – Cerebral Assessment Systems, Inc.
Safety: electrical; mechanical; chemical; thermal; radiation.	These safety issues are not applicable to this software-only device.	Electrical safety testing was performed by Canadian Standards Association. The sponsor provides a letter of attestation stating the device passed IEC 60601-1:2005. Electromagnetic compatibility was not tested.
How the device differs from Predicate device	Cantab Mobile is similar to Cognivue in terms of technological characteristics, as both electronically record objective performance as the patient responds to stimuli presented on the screen. Both tests take about 10 minutes. Cantab Mobile differs from Cognivue in that it provides an assessment of memory using one staged cognitive assessment – the Paired Associates Learning task - compared to Cognivue which includes ten short brain function tests, measuring: adaptive motor control; dynamic visual contrast sensitivity; letter, word, shape, and motion processing ability; and memory. Cantab Mobile also presents assessments of depression and activities of daily living, which are not included in Cognivue.	

Reviewer Comment: The revised Comparison Table is adequate. I have no further concerns.

Reviewer Recommendation
The Comparison of the Technology to Predicate Devices is acceptable.

VI. Labeling

Labeling Review Needed?	Yes	Undo
Usability Consult Needed?	Undo	No

Original Reviewer Comment: Labeling will be reviewed in greater detail once the sponsor provides an appropriate predicate device for comparison. Certain labeling changes have been suggested based on claims made within the labeling.

S001 Reviewer Comment: Device Labeling was reviewed and found to be acceptable.

A General Labeling Requirements

General Labeling Requirements		Inadequate or Marked
Is the prescription statement (or "Rx only") included?	Yes	☐
The indications for use are consistent with the IFU page?	Yes	☐
Appropriate contraindications, warnings, precautions and adverse events provided?	Yes	☐
Instructions are in accordance with the guidance (if applicable)?	Inapplicable	☐

Appropriate labeling inside device?	Inapplicable	☐
Appropriate label/indicator outside device?	Inapplicable	☐
Appropriate Manual labeling?	Yes	☐
Is appropriate home use information included in the labeling?	Inapplicable	☐
What MRI safety information does the labeling contain?	MR Unsafe	☐

Labeling Table: A summary of the adequacy of several labeling requirements.

Reviewer Recommendation
The provided Labeling is adequate.

VII. Reprocessing, Sterilization, and Shelf-Life

Reviewer Recommendation
Cleaning, Sterilization, Shelf-Life and Reuse descriptions are not applicable to this Device since it is software which runs on the Apple iPad tablet that is commercially available.

VIII. Biocompatibility

Reviewer Recommendation
Biocompatibility is not applicable to this device since it is software which runs on a commercially available tablet computer.

IX. Software/Firmware

Software Review Needed?	Yes	Undo
Software Consult Needed?	Undo	No

Software Documentation	Present	Absent	Inadequate
Software/Firmware Version: 1.3			
Level of Concern (LOC): Identified as Minor			☐
Software/Firmware description: **Adequacy Comments:** Adequate	☒	☐	☐
Device Hazard Analysis: **Adequacy Comments:** Adequate	☒	☐	☐
Software Requirements Specifications: **Adequacy Comments:** Adequate	☒	☐	☐
Traceability Analysis/Matrix: **Adequacy Comments:** Adequate	☒	☐	☐

Software Documentation	Present	Absent	Inadequate
Verification & Validation Testing: **Adequacy Comments:** Adequate	☒	☐	☐
Revision level history: **Adequacy Comments:** Adequate	☒	☐	☐
Software Table: Demonstrates the adequacy of the software documentation according to the Guidance Document.			

Original Reviewer Comment:

(b)(4)

(b)(4) **The sponsor will be requested to provide all sections which have been labelled inadequate above.**

S001 Reviewer Comment:

The following deficiency was sent to the sponsor regarding Software Review Documentation:

(b)(4)

a. (b)(4)

b. (b)(4)

c. (b)(4)

d. (b)(4)

e. (b)(4)

f. (b)(4)

(b)(4)

Sponsor's Response:

(b)(4)

(b)(4)

(b)(4)

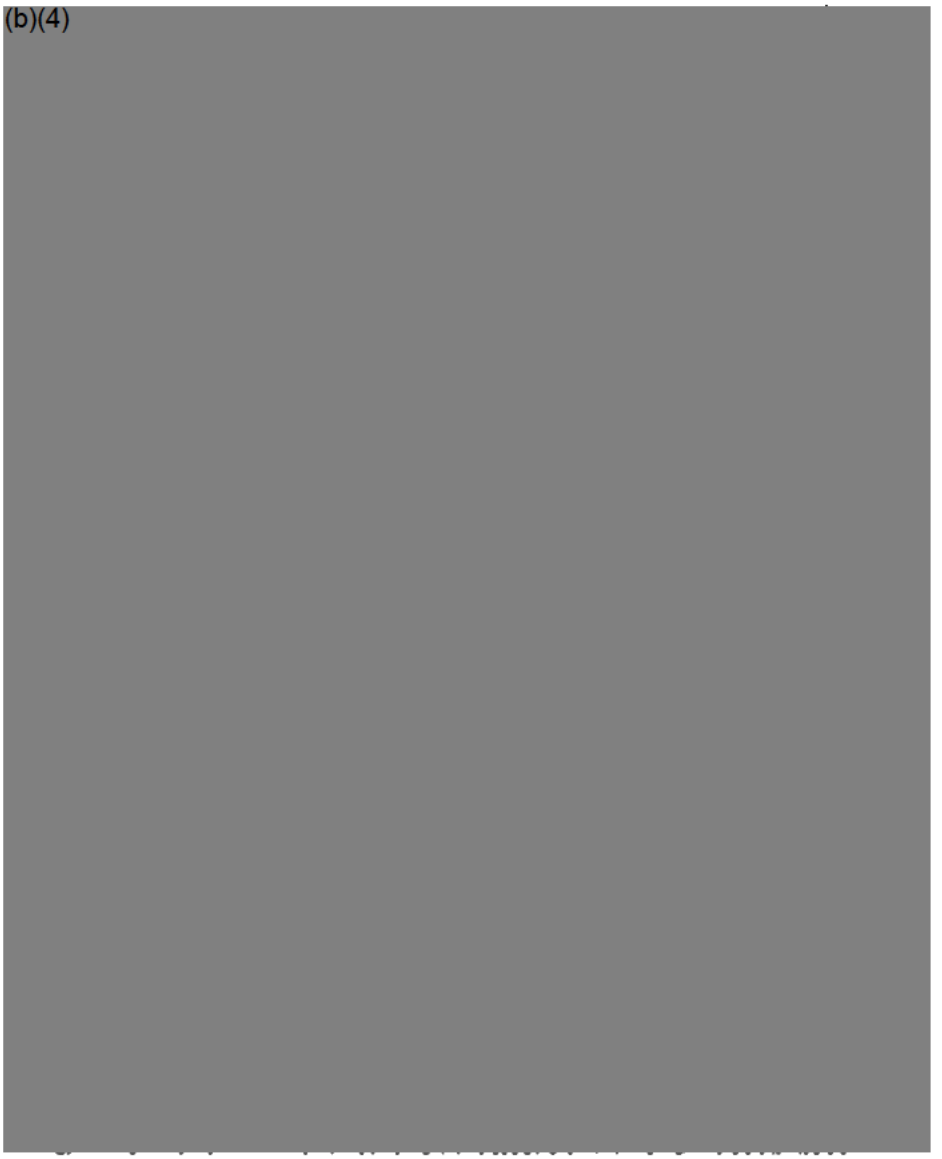


Table 2. Documents by Development and Verification Stage

	Page
(b)(4)	

S001 Reviewer Comment:
The sponsor did not provide the needed software verification and validation testing reports needed to confirm that the specified testing is appropriate. Documentation did not contain testing descriptions, pass/fail criteria, or results. The sponsor was requested to provide this information interactively and did so on January 12, 2017. Submitted testing reports were adequate. I have no further concerns/

Reviewer Recommendation
The Software is acceptable.

X. EMC & Electrical, Mechanical and Thermal Safety & Risk Analysis

EMC Review Needed?	Undo	No
EMC Consult Needed?	Undo	No

Reviewer Recommendation
The software is run off of an Apple iPad. Therefore, EMC and EMT are not needed. The sponsor will be requested to provide a Risk Analysis to support the safety of the device.

XI. Performance Testing

A Bench Testing
None Provided

Reviewer Comment: **The subject device is software which runs on the commercially available Apple iPad. Performance testing will be limited to the Software Verification and Validation testing and will be reviewed within the Software Section of this memo.**

B Animal Testing

None Provided

C Clinical Testing

(b)(4)

(b)(4)

(b)(4)

S001 Reviewer Comment:

The following deficiencies were communicated to the sponsor. Review of sponsor responses was performed by Dr. Christian Shenouda and were found to be acceptable. Please see Clinical Review memo for additional details.

- (b)(4)

  a. (b)(4)

Sponsor's Response

Note: (b)(4)

(b)(4)

(b)(4)

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

Lead Reviewer Comments:

(b)(4)

b. (b)(4)

Sponsor's Response:

(b)(4)

(b)(4)

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

Lead Reviewer Comment:

(b)(4)

(b)(4)

c. (b)(4)

Sponsor Response:

Verification and Validation testing

(b)(4)

Additional information is provided in Response to Deficiency Item 6c: Cantab Mobile Verification and Validation.

Test-retest reliability

(b)(4)

FDA REVIEWER COMMENT: The sponsor's response is adequate.

Lead Reviewer Comments:

Verification and Validation efforts were supported through results from a meta analysis of published papers. These are reported in sponsor report # (b)(4) and was supplied with this submission. The sponsor also cites two particular studies namely:

1. (b)(4)

2.

(b)(4)

In addition, on January 13, 2017 Dr. Shenouda provided the following comment via email:

In response to Tim's comment #4 (email 1/13/2017) for the CANTAB device, I reviewed the normative database and we did not obtain a stats consult. The sponsor was asked to provide a description of the normative database with demographic data and to define how cut-offs were determined. The materials provided addressed the deficiency and the sponsor also provided literature supporting use of the test for the proposed indication. The sponsor is using the test consistently with the literature and normative testing standards.

Reviewer Recommendation

The Clinical Performance Testing is acceptable.

XII. Kit Certification

This section is not usually needed. See the help text by clicking the heading.

XIII. Manufacturing Information

This section is not usually needed. See the help text by clicking the heading.

XIV. References

XV. SE Flowchart Questions

Substantial Equivalence Determination	Yes	No
Is the predicate device legally marketed?	☒	☐
Do the devices have the same intended use?	☒	☐
Please explain how the intended use of the subject device is similar to or different from the predicate device: Both devices are computer based questionaires used to assess memory.		
Do the devices have the same technological characteristics?	☒	☐

XVI. Original Deficiencies

Administrative Information

- (b)(4)
- (b)(4)

Device Description

- (b)(4)

(b)(4)

- (b)(4)
- (b)(4)

Labeling

- (b)(4)
- (b)(4)

Software

- (b)(4)
  a. (b)(4)

b. (b)(4)

c. (b)(4)

d. (b)(4)

e. (b)(4)

f. (b)(4)

These documents are necessary to ensure the safety and effectiveness of the device through adequate design and documentation. Please provide these documents.

Performance Testing

- (b)(4)

XVII. S001 Sponsor's Response to Deficiencies

Please see sections above which address various deficiencies. The sponsor has adequately addressed all deficiencies which were communicated during the original review.

XVIII. Contact History

- The sponsor was contacted Via email on 1/5/2017 requesting additional information. The following deficiencies were communicated:

  a. (b)(4)

  b. (b)(4)

  The sponsor responded to this request on 1/6/2017.

- (b)(4)

- (b)(4)

Digital Signature Concurrence Table	
Reviewer Sign-Off	Binoy J. Mathews -S Digitally signed by Binoy J. Mathews -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013396044, cn=Binoy J. Mathews -S Date: 2017.01.13 14:20:10 -05'00'