



[www.ep-ad.org](http://www.ep-ad.org)

**European Prevention of Alzheimer's Dementia Consortium**  
*Grant Agreement n°115736*

# **D1.5 Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study**

**WP1 – Scientific Challenges**


**V2.0**  
*Final version*

Lead beneficiary: University of Oxford

Date: 10/08/17


Nature: Report

Dissemination level: PU

	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges	<b>Version:</b> v2.0 – Final version	
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1	<b>Security:</b> PU	2/11

## TABLE OF CONTENTS

<b>DOCUMENT INFORMATION .....</b>	<b>3</b>
<b>DOCUMENT HISTORY .....</b>	<b>4</b>
<b>DEFINITIONS .....</b>	<b>5</b>
<b>ABBREVIATIONS.....</b>	<b>7</b>
<b>EXECUTIVE SUMMARY .....</b>	<b>8</b>
<b>1. OPERATIONALIZATION OF THE SAG RECOMMENDATIONS IN THE LONGITUDINAL COHORT STUDY .....</b>	<b>9</b>
1.1. CLINICAL AND COGNITIVE OUTCOMES SAG.....	9
1.2. FLUID BIOMARKERS SAG REPORT .....	10
1.3. IMAGING SAG REPORT .....	10

 EPAD - 115736	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges		<b>Version:</b> v2.0 – Final version
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1		<b>Security:</b> PU

## DOCUMENT INFORMATION

<b>Grant Agreement Number</b>	115736	<b>Acronym</b>	EPAD
<b>Full title</b>	Prevention of Alzheimer’s Dementia Consortium		
<b>Project URL</b>	www.ep-ad.org		
<b>IMI Project officer</b>	Elisabetta Vaudano (elisabetta.vaudano@imi.europa.eu)		

<b>Deliverable</b>	D1.5	<b>Title</b>	Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study
<b>Work package</b>	WP1	<b>Title</b>	Scientific Challenges

<b>Delivery date</b>	<b>Contractual</b>	Month 30	<b>Actual</b>	10/08/17
<b>Status</b>	Current version / V2.0		Draft <input type="checkbox"/> Final <input checked="" type="checkbox"/>	
<b>Nature</b>	Report <input checked="" type="checkbox"/> Prototype <input type="checkbox"/> Other <input type="checkbox"/>			
<b>Dissemination Level</b>	Public <input checked="" type="checkbox"/> Confidential <input type="checkbox"/> Other <sup>1</sup> <input type="checkbox"/>			

<b>Authors (Partner)</b>	David Ruvolo (UOXF), Silvia Ingala (VUMC), Maartje Meijer (IXICO), Sindhuja Muskaar (Accenture), Andrew Satlin (EISAI), Gary Romano (JPNV), and Simon Lovestone (UOXF) on behalf of WP1		
<b>Responsible Author</b>	David Ruvolo	<b>Email</b>	<a href="mailto:David.ruvolo@psych.ox.ac.uk">David.ruvolo@psych.ox.ac.uk</a>
	<b>Partner</b> UOXF	<b>Phone</b>	+44 (0) 1865 613176


<b>Description of the deliverable</b>	Re-assessment of key readouts and recommendations from SAGs
<b>Key words</b>	EPAD, Biomarkers, Clinical Assessments, Outcome Measures, Longitudinal Cohort Study

*Confidential Information (please indicate here if any sections contain confidential information and should NOT be made publically available)*

<b>Relevant Section(s)</b>	1. Title or 1.1 Subtitle level 2 or 1.1.1 Subtitle level 3
----------------------------	--


<b>Does the Executive Summary contain confidential information</b>	No
<b>Can the Executive Summary be published online</b>	Yes

<sup>1</sup> If “Other” type of dissemination level, please inform the PMO team ([mgt@ep-ad.org](mailto:mgt@ep-ad.org)) accordingly.

 EPAD - 115736	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges		<b>Version:</b> v2.0 – Final version
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1		<b>Security:</b> PU

## DOCUMENT HISTORY


NAME	DATE	VERSION	DESCRIPTION
David Ruvolo (UOXF), Silvia Ingala (VUMC), Maartje Meijer (IXICO), Sindhuja Muskaar (Accenture), Andrew Satlin (EISAI), Gary Romano (JPNV), and Simon Lovestone (UOXF)	12/10/16	1.0	Outline
David Ruvolo (UOXF), Silvia Ingala (VUMC), Maartje Meijer (IXICO), Sindhuja Muskaar (Accenture), Andrew Satlin (EISAI), Gary Romano (JPNV), and Simon Lovestone (UOXF)	01/06/17	1.1	First Draft
David Ruvolo	13/06/17	1.1	Internal Review
Lennert Steukers	15/06/17	1.2	Final Draft- External review
Laura Carrera Carballés	19/07/17	1.3	Consortium Review
Laura Carrera Carballés	10/08/2017	2.0	Final version

 EPAD - 115736	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges		<b>Version:</b> v2.0 – Final version
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1		<b>Security:</b> PU


## DEFINITIONS<sup>2</sup>

- Partners of the EPAD Consortium are referred to herein according to the following codes:
  - **Janssen.** Janssen Pharmaceutica NV (Belgium)
  - **UEDIN.** The University of Edinburgh (United Kingdom)
  - **UOXF.** Masters and Scholars of the University of Oxford (United Kingdom)
  - **BBRC.** BarcelonaBeta Brain Research Center (Spain)
  - **SYNAPSE.** Synapse Research Management Partners S.L (Spain)
  - **KI.** Karolinska Institutet (Sweden)
  - **VU-VUMC.** Stichting VU-VUmc (Netherlands)
  - **UCAM.** Masters and Scholars of the University of Cambridge (United Kingdom)
  - **MRC.** Medical Research Council (United Kingdom)
  - **BERRY.** Berry Consultants LLP (United Kingdom)
  - **UNIGE.** Université de Genève (Switzerland)
  - **RUMC.** Stichting Katholieke Universiteit (Netherlands)
  - **CU.** Cardiff University (United Kingdom)
  - **CHUT.** Centre Hospitalier Universitaire de Toulouse (France)
  - **QUINTILES.** Quintiles, Ltd (United Kingdom)
  - **AE.** Alzheimer Europe (Luxemburg)
  - **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
  - **APHP.** Hôpital de la Salpêtrière (France)
  - **INSERM.** Institut National de la Santé et de la Recherche Médicale (France)
  - **ULEIC.** University of Leicester (United Kingdom)
  - **IXICO.** IXICO Technologies Ltd (United Kingdom)
  - **ARACLON.** Araclon Biotech S.L (Spain)
  - **FRAUNHOFER.** Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V. (Germany)
  - **Eisai.** Eisai Inc (United States)
  - **SARD.** Sanofi-Aventis Recherche & Développement (France)
  - **NOV.** Novartis Pharma AG (Switzerland)
  - **BI.** Boehringer Ingelheim International GmbH (Germany)
  - **Eli Lilly.** Eli Lilly and Company Ltd (United Kingdom)
  - **HLU.** H. Lundbeck A/S (Denmark)
  - **Takeda EU.** Takeda Development Centre Europe Ltd (United Kingdom)
  - **AC Immune.** AC Immune SA (Switzerland)
  - **Biogen.** Biogen Idec Limited (United Kingdom)
  - **Amgen.** Amgen NV (Belgium)
  - **Pfizer.** Pfizer Limited (United Kingdom)
  - **UCB.** UCB Biopharma SPRL (Belgium)
  - **ARIDHIA.** Aridhia Informatics Ltd (United Kingdom)
  - **ROCHE.** F. Hoffmann - La Roche (Switzerland)

<sup>2</sup> To be completed with terms and abbreviations related to the actual content of the document

 EPAD - 115736	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges	<b>Version:</b> v2.0 – Final version	
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1	<b>Security:</b> PU	6/11


- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the EPAD project (115736).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The EPAD Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst EPAD participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

 EPAD - 115736	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges		<b>Version:</b> v2.0 – Final version
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1		<b>Security:</b> PU

## ABBREVIATIONS

Abbreviations used throughout the document are listed below.

- **AD.** Alzheimer's Dementia
- **ADL.** Activities of Daily Living
- **ASL.** Arterial Spin Labeled MRI
- **CCO-SAG.** Clinical and Cognitive Outcomes Scientific Advisory Group
- **CCSC.** Clinical Compound Selection Committee
- **CDR.** Clinical Dementia Rating Scale
- **CSF.** Cerebrospinal Fluid
- **D1.x.** Deliverable by WP1. Number x.
- **DTI.** Diffusion Tensor Imaging
- **EPAD.** European Prevention of Alzheimer's Disease
- **ENE.** EPAD Neuropsychological Evaluation
- **FLAIR.** Fluid Attenuation Inversion Recovery
- **fMRI.** Functional MRI
- **GDS.** Geriatric Depression Scale
- **IADL.** Instrumental Activities of Daily Living
- **LCS.** Longitudinal Cohort Study
- **MRI.** Magnetic Resonance Imaging
- **PCs.** Parent Cohorts
- **PCE.** Primary Cognitive Endpoint
- **PoC.** Proof of Concept; as in the EPAD Proof of Concept study
- **RBANS.** Repeatable Battery for the Assessment of Neuropsychological Status
- **rs-fMRI.** Resting state functional MRI
- **SAG(s).** Scientific Advisory Group(s)
- **SOG.** Site Operations Guide (Imaging)
- **SWI.** Susceptibility Weighted Imaging
- **TDC(s).** Trial Delivery Centre
- **WPx.** Work Package *number* (ex: WP1, WP2, etc.)

	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges		<b>Version:</b> v2.0 – Final version
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1		<b>Security:</b> PU

## EXECUTIVE SUMMARY


The objective of this document, Deliverable 1.5 (D1.5) – “Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study” —is to present the re-assessment of key outcomes and recommendations for the EPAD Longitudinal Cohort Study (LCS). These recommendations were developed by the Scientific Advisory Groups (SAGs) and originally presented in Deliverable 1.1<sup>3</sup>, and then later modified in Deliverable 1.3<sup>4</sup>.

This document will provide an overview of the re-assessment of SAG recommendations. This includes the optimization of the EPAD Neuropsychological Evaluation (ENE) Battery by the Clinical and Cognitive Outcomes SAG (CCO-SAG), which summarizes the definitions of the Primary Cognitive Endpoint (PCE) and secondary outcomes. This section will also include an overview of work towards defining the CSF analytic plan led by the Fluid Biomarkers group. The final section will provide details of the operationalization of the imaging recommendations for the development of the Site Operations Guide (SOG). This includes the protocol parameters for the core and advanced protocol and the revision of quality control duties. There are no changes the recommendations made by the genetics or epidemiology SAG.

<sup>3</sup> Deliverable 1.1: Evaluation of pre-clinical and prodromal diagnostic criteria, risk spectrum and inclusion criteria for the Register and Cohort

<sup>4</sup> Deliverable 1.3: Interim Report on Biomarkers, Clinical Assessments, and Outcome Measures



 EPAD - 115736	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges		<b>Version:</b> v2.0 – Final version
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1		<b>Security:</b> PU

# 1. Operationalization of the SAG Recommendations in the Longitudinal Cohort Study

## 1.1. Clinical and Cognitive Outcomes SAG

The Clinical and Cognitive Outcomes Scientific Advisory Group’s (CCO-SAG) recommendations for the neuropsychological assessment of participants in EPAD were published in the journal *Alzheimer’s & Dementia*<sup>5</sup>. Evidence and rationale for the recommendations for the development of the EPAD Neuropsychological Evaluation battery is provided in the systematic review produced by the group in early 2015. Since then, this work was also accepted for publication in *Alzheimer’s & Dementia*<sup>6</sup>.

For the first LCS protocol amendment, the group optimized the EPAD Neuropsychological Evaluation (ENE), which included re-defining the cognitive outcomes for the Repeatable Battery for the Assessment of Neuropsychological Status (see table 1) and updating the cognitive measures and administration overview<sup>7</sup>.


Table 1. CCO-SAG Outcomes for the LCS: RBANS

Category	Name	Included Tasks
Primary	RBANS Total Scale Index Score	All RBANS tasks
	Immediate Memory Index	List Learning, Story Memory
Secondary	Visuospatial/Constructional Index	Figure Copy, Line Orientation
	Language Index	Picture Naming, Semantic Fluency
	Attention Index	Digit Span, Coding
	Delayed Memory Index	List Recall, List Recognition, Story Recall, Figure Recall

<sup>5</sup> Ritchie, K., Ropacki, M., Albala, B., Harrison, J., Kaye, J., Kramer, J., Randolph, C., and Ritchie, C. (2017). Recommended cognitive outcomes in preclinical Alzheimer’s disease: Consensus statement from the European Prevention of Alzheimer’s Dementia project. *Alzheimer’s & Dementia*, 13(2), 186-195. <http://dx.doi.org/10.1016/j.jalz.2016.07.154>

<sup>6</sup> Mortamais, M., Ash, JA, Harrison, J., Kaye, J., Kramer, J., Randolph, C., Pose, C., Albala, B., Ropacki, M., Ritchie, C., and Ritchie, K. (2017). Detecting cognitive changes in preclinical Alzheimer’s disease: A review of its feasibility. *Alzheimer’s & Dementia*, 13(4), 468-492. <http://dx.doi.org/10.1016/j.jalz.2016.06.2365>

<sup>7</sup> EPAD LCS Protocol section 3.4.1.1+

 EPAD - 115736	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges		<b>Version:</b> v2.0 – Final version
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1		<b>Security:</b> PU

The primary cognitive endpoint (PCE) in the LCS is the RBANS Total Scale Index Score. The PCE was chosen based on the acceptance status by regulatory authorities for use in clinical trials. The RBANS will serve as a comparable measure for validation studies—e.g., validation studies of alternate forms, normative data—on secondary (Dot Counting, Flanker, Favourites) and exploratory (Four Mountains Task, Supermarket Trolley) measures.

## 1.2. Fluid Biomarkers SAG Report

The fluid biomarkers group has considered the use of CSF markers of Abeta and tau for use in the LCS. For this phase of the programme, a review of the available platforms for analysis was performed led by Kaj Blennow (University of Gothenburg). Taking into consideration technical and other performance aspects of alternative platforms, the SAG recommended the primary biomarker outcomes for the LCS are A $\beta$ , t-tau, and p-tau. This recommendation was made to the Executive committee, which was accepted and is now implemented in the LCS protocol. The technical recommendations for CSF processing were implemented into the EPAD Sample Instruction Manual.


In addition to a recommendation of platform choice, the fluid biomarkers SAG has advised on the performance of the chosen platform in relation to cut-offs for diagnosis.

## 1.3. Imaging SAG Report

Since the recommendations outlined in D1.1, the imaging group has focused on the operationalization of the imaging protocol. The primary tasks were to define imaging parameters for the EPAD Imaging protocol and to develop procedures for participant eligibility and safety and quality control. The SAG membership was expanded to include members from IXICO.

### *Protocol Parameters for Core and Advanced Sequences*

For the Longitudinal Cohort Study (LCS), participants may undergo the core (3D T1W, 3D FLAIR /2D FLAIR, 2D-T2\*, 2D T2) and advanced (3D SWI/3D T2\*, rs-fMRI, ASL, DTI and field map) imaging protocol at baseline and annual visits. All sites are expected to implement the core protocol in accordance with the sequence parameters list in the Site Operations Guide, whereas the advanced sequences are optional and/or sites may implement a portion of the protocol dependent on site facilities and resources. All TDCs implement the MR protocol according to local setup, which is verified after review of phantom or healthy

 EPAD - 115736	<b>D1.5</b> Interim Report on the Scientific Recommendations and Key Outcomes for the Longitudinal Cohort Study		
	<b>WP1.</b> Scientific Challenges		<b>Version:</b> v2.0 – Final version
	<b>Author(s):</b> David Ruvolo, Silvia Ingala, Maartje Meijer, Michael Ropacki, Sindhuja Muskaar, Andrew Satlin, Gary Romano, and Simon Lovestone on behalf of WP1		<b>Security:</b> PU

volunteer<sup>8</sup> acquisitions. Verification includes a review of all parameters—defined in section 4 of the SOG—to ensure they were implemented correctly.

*Revision of Quality Control Duties: Participant Safety and Exclusion*

During and following image acquisition, all TDCs are asked to review images for quality control (guidelines can be found in the EPAD LCS SOG<sup>9</sup>). Local imaging teams must look for the following: 1) areas where there is a lack of full coverage, 2) no heavy motion artefacts, 3) significant intensity inhomogeneity, 4) poor signal to noise ratio and 5) any other artefacts that may impact image quality. If impact quality is suboptimal, the TDC can decide to acquire a rescan whilst the subject is still in the scanner. Following local quality control procedures, all images are uploaded to IXICO’s central data repository, which initiates the EPAD-IXICO Quality Control Process.

After successful upload of the data, an IXICO analyst will perform a quality control of the data. This includes a check to see if the data is complete (i.e. no missing sequences) and whether the metadata is consistent with the implemented EPAD protocol parameters. If the QC fails at this point, a query is sent back to the site requesting clarification and/or re-upload of the data. If the QC is successful, then the data is sent for radiological reading. The radiological readers will subsequently perform a visual QC of the images.

Radiological reads of all scans will be a joint effort by an EPAD Radiologist based at the University of Edinburgh and Vrije Universiteit (VU) Medical Center of Amsterdam. The purpose is to evaluate if study participants meet criteria for inclusion or any findings that may affect a participant’s participation in the LCS<sup>10</sup>.

During the visual QC by the radiologists, rescans may be requested if the quality of images is poor. However, all rescans are determined by the willingness of the participant and the TDC’s capabilities to perform rescans. The radiologist may also provide feedback on image quality to the site in order to improve this for future scans.

<sup>8</sup> All TDCs must have ethical approval and meet other local requirements in order to conduct a test scan involving a health participant.

<sup>9</sup> See EPAD LCS Site Operations Guide Appendix C: “On Site Image Quality Review Guidance” for further TDC QC procedures.

<sup>10</sup> Criteria may be revised over time. Please consult the appendices in the LCS Site Operations Guide.