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European Prevention of Alzheimer's Dementia Consortium
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D1.3 Interim Report on Biomarkers, Clinical Assessments, and Outcome Measures

WP1 – Scientific Challenges

V1.0
Final

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	WP1 – Scientific Challenges		Version: v1.0 –Final
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DOCUMENT INFORMATION

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Authors (Partner)	David Ruvolo (UOXF), Andy Satlin (Eisai), Bruno Dubois (APHP), Carol Brayne (UCAM), Frederik Barkhof (VU-Vumc), Gary Romano (JPNV), Julie Williams (CU), Karen Ritchie (INSERM), Simon Lovestone (UOXF), with SAG members		
Responsible Author	David Ruvolo	Email	David.ruvolo@psych.ox.ac.uk
	Partner UOXF	Phone	+44 (0) 1865 613176

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DEFINITIONS

- 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, Inc (United States)
 - **Amgen.** Amgen NV (Belgium)
 - **Pfizer.** Pfizer Limited (United Kingdom)
 - **UCB.** UCB Biopharma SPRL (Belgium)
- **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.

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ABBREVIATIONS

Abbreviations used throughout the document are listed in the table below.

- **AD.** Alzheimer's Dementia
- **CCO-SAG.** Clinical and Cognitive Outcomes Scientific Advisory Group
- **D1.x.** Deliverable by WP1. Number *x*.
- **EPAD.** European Prevention of Alzheimer's Disease
- **ECE.** EPAD Cognitive Evaluation
- **GAP.** Global Alzheimer's Platform
- **LCS.** Longitudinal Cohort Study
- **PCs.** Parent Cohorts
- **PoC.** Proof of Concept
- **RBANS.** Repeatable Battery for the Assessment of Neuropsychological Status
- **SAG(s).** Scientific Advisory Group(s)
- **SNPs.** Single Nucleotide Polymorphisms
- **TDC(s).** Trial Delivery Centre
- **WP.x.** Work Package *number* (ex: WP1, WP2, etc.)

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EXECUTIVE SUMMARY

The purpose of this document, Deliverable 1.3 (D1.3) - “The Interim Report,” is to report on the proposed biomarkers, clinical assessments, and outcome measures that were recommended by the Scientific Advisory Groups (SAGs) for use in the EPAD Longitudinal Cohort Study (LCS; outlined in Deliverable 1.1, Section 3).

This document is divided into two sections:

1. The first section provides a brief summary on the recommendations proposed in D1.1 for the EPAD Longitudinal Cohort Study (LCS; pg. 8).
2. Section two reports on the inclusion of the SAG recommendations for use in the LCS.

Further information and links to supporting documentation can be found in the annex 1.

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1. Background

In Deliverable 1.1,¹ the SAGs presented recommendations for EPAD register and the EPAD Longitudinal Cohort Study (LCS). The recommendations for the register are based largely on expert opinion whereas the LCS advice is comprised of evidence-based recommendations derived from synthesis of the literature and analysis of criteria using pre-existing datasets. The scientific advice was designed to recruit participants on a “risk spectrum,” which is defined as individuals who have evidence of or are at risk for developing Alzheimer’s Dementia (AD), but who are asymptomatic or mildly symptomatic though not demented.

A summary of the recommendations for the LCS that were presented in D1.1 can be found table 1 and references for all supporting documentation can be found in annex 1.

Table 1. Recommendations for the EPAD LCS as presented in D1.1 by Scientific Advisory Group

Group	Recommendation
Clinical and Cognitive Outcomes	The Clinical and Cognitive Outcomes SAG recommends annual administration of the EPAD Cognitive Evaluation (ECE) battery to all participants in the LCS.
Fluid Biomarkers	The Fluid Biomarkers SAG recommends inclusion of CSF measures of AD pathology (A β , Tau and pTau) for all participants selected into the LCS, as this data will be used for modelling risk of dementia and for staging of disease pathology.
Genetics	The Clinical SAG recommends exploring the potential of Polygenic Scores (PS) for risk evaluation. Where genome wide SNP data is available, where available data should be obtained and where not genotyping at PRS Loci should be considered.
Imaging	The Imaging SAG recommends 1) if resources allow, it is suggested Amyloid-PET at screening for all participants and a sizeable subset at year two, 2) Structural MRI in all participants at baseline and at yearly intervals, and 3) ASL and resting-state fMRI in a sizeable subset at baseline and at year two.
WP1	It is preferred that global assessments such as MMSE and CDR be integrated into the inclusion examination as clinical descriptors as these measures are regularly used in studies and in some cases are regulatory authority approved measures of clinical state.

Note: Items in table 1 may differ than the items listed in table 2 as these tables are illustrating the changes in WP1 recommendations from D1.1 into the LCS protocol.

¹ Deliverable 1.1 - “Evaluation of pre-clinical and prodromal diagnostic criteria, risk spectrum and inclusion criteria for Register and Cohort” <https://epadpm.teamwork.com/files/1885537>

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2. Inclusion of Recommendations for the EPAD LCS

The purpose of this section is to provide an overview of the inclusion of SAG recommendations for use in the Longitudinal Cohort Study (LCS; the changes to the recommendations presented in D1.1). The SAG recommendations (biomarkers, clinical assessments, and outcome measures) for use in the LCS occurred over a series of discussions from July – October 2015 between SAGs with WP1 and the EPAD delivery cluster (WP2, 3, and 4) as well as the larger EPAD community including Global Alzheimer’s Platform (GAP) partners. Further information on the measures included LCS can be found in Annex 1.

Table 2. Inclusion of WP1 Recommendations into the Final Data Collection Protocol for the EPAD Longitudinal Cohort Study

Group	Protocol	Module	Procedures	Frequency
Clinical and Cognitive Outcomes	EPAD Cognitive Evaluation (ECE)	Primary	RBANS Battery	All Visits
		Secondary	Dot Counting, Flanker, Name-face Pairs	All Visits
		Exploratory	Four Mountains Virtual Reality Supermarket Trolley	All Visits
	Clinical Measures	Clinical	GDS, STAI, Pittsburgh Sleep Quality Index, Amsterdam IADL	Screening/Baseline + Annual Follow Ups
Biomarkers & Genetics	Specimens	---	Blood and CSF sampling	Screening/Baseline + Annual Follow Ups
Imaging	Imaging	Standard	Structural (3D-TI, 3D-FLAIR, 2D-T2, 2D- or 3D-SWI)	Screening/Baseline + Annual Follow Ups
		Subset	Structural (DTI) + Functional (ASL, rsfMRI)	Screening/Baseline + Annual Follow Ups
WP1	Other Clinical Measures	---	Dementia Diagnosis, CDR	All Visits
			MMSE	Screening/Baseline + Annual Follow Ups

Note: In the following sections, the stating of “protocol”, “module”, or “procedures” is referring to the column headers in table 2. Items in table 2 may differ than the items listed in table 1 as these tables are illustrating the changes in WP1 recommendations from D1.1 into the LCS protocol.

2.1.WP1 Report

The Clinical Dementia Rating scale (CDR) will be administered to all participants at all visits. The Mini Mental Status Exam (MMSE) will be administered to all participants at all visits except at the six-month follow up visit. It was recommended to include these measures as they are regularly used in studies and are regulatory authority approved measures of clinical state.

2.2.Clinical and Cognitive Outcomes SAG Report

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All participants in the LCS will be administered the EPAD Cognitive Evaluation battery (ECE; primary, secondary, and exploratory modules) at all visits using a tablet by a trained clinical rater. MedAvante was recommended as the organization of choice for overseeing electronic cognitive assessment in the LCS and PoC. They will oversee the training of all clinical raters in accordance with the standard procedures of each measure as defined by the test developers and coordinate the data collection process. As a regulatory approved provider (FDA and EEMA), MedAvante’s Virgil[®] Investigative Study Platform fulfills the requirements of the EPAD Cognitive Evaluation (ECE) developed by the Clinical and Cognitive advisory group, while ensuring standardization across study centers. Primary reasons for selecting MedAvante include experience with electronic cognitive assessment, measures included in the ECE are already programmed for tablet-based assessment in multiple languages, and for experience with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which was selected for the primary cognitive outcome measure in the PoC. The clinical measures module (i.e., GDS, STAI, etc.) will not be administered at the six-month visit.

The measures were selected based on the greatest possible sensitivity to pre-clinical changes, cross-cultural transferability, and availability of parallel forms, while also providing both accuracy and processing time measures. In addition, these tests were chosen with consideration for whether a test would integrate well within a total battery administration time of no more than one hour. Further information on the criteria and information used to select each measure can be found in the links provided in annex 1.

The ECE was developed as modules (primary, secondary, exploratory, and clinical) with the intention that the battery may be customized for each pharmaceutical target nominated into the PoC (i.e., a subset of modules). The secondary and exploratory tests target cognitive domains not covered by RBANS and considered by the CCO SAG to be implicated in the earliest preclinical phases. The selection of cognitive and clinical measures is dependent on future agreements between EPAD and compounds owners, which will occur as compounds are nominated for use in the PoC². The primary battery, RBANS, will be administered to all participants enrolled into the PoC, as the RBANS total score will be used as the primary outcome measure.

The Clinical and Cognitive Outcomes SAG along with members from WP2 developed the EPAD primary cognitive outcome measure (the RBANS total score), which will be used to measure the rate of progression of cognitive decline in the PoC. The RBANS consists of 12 subtests that are used to calculate five index scores and summed as a total score. Test indices are Immediate Memory (comprising List Learning and Story Memory tasks), Visuospatial/Constructional (comprising Figure Copy and Line Orientation tasks), Language (comprising Picture Naming and Semantic Fluency tasks), Attention (comprising Digit Span and Coding tasks), and Delayed Memory (comprising List Recall, Story Recall, Figure Recall, and List Recognition tasks). Each index score is expressed as an age-adjusted standard score with a mean of ~100 and an SD of ~15.

2.3.Fluid Biomarkers SAG Report

CSF sampling in the LCS will occur for all participants at baseline and all annual visits. The Biomarkers SAG recommended using the Roche Diagnostics assay for the assay’s strong performance in relation to similar assays (i.e., strong correlation with other assays, minimal inter-batch variability) and for alignment with parallel projects (ADNI, etc.). All CSF processing will take place at facilities directed by Kaj Blennow

² Deliverable 1.2 produced by the CCSC documents the compound selection process and the criteria used to nominate compounds (<https://epadpm.teamwork.com/files/2141396>)

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and follow the standardized procedures already used by that facility. Official documentation for procedures relating to CSF collection, handling, and storage is forthcoming.

Blood in the LCS will occur at all visits except the six-month follow up for all participants. Justification for the collection of blood for future exploratory studies of blood-based biomarkers can be found in D1.1 (see link in annex 1). Samples were recommended for routine collection and storage for future exploratory studies of validating biomarkers putative blood-based biomarkers and to further develop novel markers of considerable potential utility in EPAD and future clinical trials. Standard Operating Procedures for collection and curation of non-CSF samples established for the AddNeuroMed programme were reviewed by members of WP1 and then by Sid O’Bryant (Alzheimer’s Association Professional Interest Association Blood based Biomarkers lead) in the context of a harmonisation process for such SOPs. This SOP is under review by the Clinical Development Group and the EPAD Executive committee.

2.4.Genetics SAG Report

Regarding polygenic scores, item three of the Genetics SAG³ recommendations document was modified to:

“...Participants in the LCS should be genotyped, as part of exploratory studies, for the Single Nucleotide Polymorphisms (SNPs) contributing to a polygenic score established by Cardiff University, for replication and validation purposes and so this information will be available for potential use in selecting PoC populations for specific interventions for which such selection might be appropriate or useful.”

2.5.Imaging SAG Report

All participants will undergo the standard imaging module⁴ at baseline and annual visits. Only a subset of participants will receive the subset imaging module⁵, which will be determined by the resources of each Trial Delivery Centre (TDCs), coordinated by WP4⁶. The change of frequency in fMRI from the original recommendations (baseline and at year two) to the LCS protocol (baseline and annually) occurred during discussions between the Imaging SAG and LCS protocol writing team and is likely attributed to the additional resources that would have gone to amyloid imaging protocol.

In D1.1, the Imaging SAG recommended Amyloid-PET imaging for all participants at screening into the LCS and again at year two for a subset of the cohort (see table 1; consult the imaging SAG recommendations document for background information or D1.1, links are provided in annex 1). During the development of the LCS protocol, it was determined that resources would not allow for Amyloid-PET imaging for the amount of participants at the proposed frequency. Thus, amyloid imaging was not included in the LCS protocol (see table 2). Given the evidence of Amyloid detection in the CSF and the frequency of CSF collection in the LCS, this would supplement Amyloid Imaging. Currently, the Imaging SAG has a grant application for the IMI-2 call 5, which would establish Amyloid Imaging to Prevent Alzheimer’s Disease (AMYPAD) and allow EPAD to perform additional imaging. As of December 2015, this application progressed to stage two of the IMI review process. A summary of the grant proposal can be found on the

³ Referencing the Genetics SAG recommendations document. Links are provided in genetics section of Annex 1

⁴ The use of standard imaging procedures is referring to the set of scans listed in table 2

⁵ The use of subset imaging procedures is referring to the set of scans listed in table 2

⁶ See imaging recommendations for further information (link provided in Annex 1/Imaging/Recommendations)

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[Alzheimer's Europe](#) site and a copy of the stage 1 proposal is available [here](#). Information regarding image processing, storage, and accessibility will appear in the Imaging SAG white paper.

Annex 1. Additional Resources

This report was written to provide an overview of the inclusion of the SAG recommendations into the LCS protocol whereas greater detail can be found in one of the following documents (see below).

- **Deliverable 1.1** - “Evaluation of pre-clinical and prodromal diagnostic criteria, risk spectrum and inclusion criteria for Register and Cohort”. This documents provides an overview of the recommendations developed by the SAGs and a summary of the evidence to support these recommendations. For SAG specific documentation, they are listed in below. The final version of D1.1 can be found here: <https://epadpm.teamwork.com/files/1885537>
- **Clinical and Cognitive Outcomes SAG**
 - CCO-SAG White Paper: <https://epadpm.teamwork.com/files/1795943>
 - CCO-SAG Review: <https://epadpm.teamwork.com/files/1603387>
 - Cognition Library: <https://epadpm.teamwork.com/projects/63360/files?catId=124210>
- **Imaging**
 - Recommendations: <https://epadpm.teamwork.com/files/1795942>
 - Literature Review: <https://epadpm.teamwork.com/files/2158553>
 - Library of Evidence: <https://epadpm.teamwork.com/files/2158554>
- **Genetics**
 - Recommendations: <https://epadpm.teamwork.com/files/2001737>
 - Genetics Review: <https://epadpm.teamwork.com/files/2001738>
 - Supplementary Tables: <https://epadpm.teamwork.com/files/2001739>
 - Recommendations Slide set: <https://epadpm.teamwork.com/files/2001740>