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Evaluation of pre-clinical and prodromal diagnostic criteria, risk spectrum and inclusion criteria for Register and Cohort

WP1 – Scientific Challenges

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TABLE OF CONTENTS

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Description of the deliverable	The purpose of this document is to present the evaluation of pre-clinical and prodromal diagnostic criteria, risk spectrum and inclusion criteria for Register and Cohort developed by WP1 SAGs.
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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.** Boehriger 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.

Abbreviations

Abbreviations used throughout the document are listed below.

- **AD.** Alzheimer's Disease
- **ADL.** Activities of Daily Living
- **ADNI.** Alzheimer's Disease Neuroimaging Initiative
- **APOE.** Apolipoprotein E
- **APP.** Amyloid Precursor Protein
- **ARWMC.** Age-related White Matter Changes
- **ASL-MRI.** Arterial Spin Labelled MRI
- **BP.** Binding Potential
- **CCO-SAG.** Clinical and Cognitive Outcomes Scientific Advisory Group
- **CCSC**. Clinical Compound Selection Committee
- **CDR.** Clinical Dementia Rating scale
- **CSF.** Cerebrospinal fluid
- **DFM.** Default Mode Network
- **DTI.** Diffusion Tensor Imaging
- **EEG.** Electroencephalography
- **EMIF.** European Medical Information Framework
- **EPAD**. European Prevention of Alzheimer's Disease
- **FA.** Fractional Anisotropy
- **FDG-PET.** Fluorodeoxyglucose Positron Emission Tomography
- **FLAIR.** Fluid Attenuation Inversion Recovery
- **fMRI.** Functional MRI
- **GAP.** Global Alzheimer's Platform
- **GDS.** Geriatric Depression Scale
- **GWAS.** Genomic Wide Associative Studies
- **HMPAO-SPECT.** Hexamethylpropyleneamine Oxime Single-photon Emission CT
- **IADL.** Instrumental Activities of Daily Living
- **IMI.** Innovative Medicines Initiative
- **ISTAART.** International Society to Advance Alzheimer's Research and Treatment
- **LCS**. Longitudinal Cohort Study
- **MCI.** Mild Cognitive Impairment
- **MEG.** Magnetoencephalography
- **MMSE.** Mini Mental Status Exam
- **MRI.** Magnetic Resonance Imaging
- **PCs.** Parent Cohorts
- **PoC**. Proof of Concept
- **PS.** Polygenic Scores (see Genetics SAG)
- **RBANS.** Repeatable Battery for the Assessment of Neuropsychological Status
- **ROI.** Regions of Interest
- **rsfMRI.** Resting State fMRI
- **SAG(s)**. Scientific Advisory Group(s)
- **SCI.** Subjective Cognitive Impairment
- **SMC.** Subjective Memory Complaints
- **SNP.** Single Nucleotide Polymorphisms
- **STAI.** State-Trait Anxiety Inventory
- **SUVR.** Standardized Uptake Value
- **WM.** White Matter
- **WP***x*. Work Package *number* (ex: WP1, WP2, etc.)

Executive Summary

The purpose of this document, Deliverable 1.1 - "Defining the Evaluation Criteria," is to present the recommendations for the EPAD Register and EPAD Longitudinal Cohort Study (LCS) developed by the Scientific Advisory Groups (SAGs). These recommendations will be used to create a procedure for recruiting participants from pre-existing parent cohorts (PCs) into the EPAD Register (overseen by WP3), which will serve as the main recruitment source for the LCS. Once selected into the LCS according to the advice outlined in section two (the LCS protocol, coordinated by WP4), participants will undergo the assessments proposed in that section and potentially be recruited into a Proof of Concept trial (PoC).

This document is divided into three sections:

1. The first section provides a background of WP1—structure, composition, and primary objectives of the SAGs—and concludes by defining the risk spectrum.

2. Section two summarizes the recommendations for the register developed by the five SAGs (Clinical and Cognitive Outcomes, Epidemiology, Fluid Biomarkers, Genetics, and Imaging), based largely on expert opinion and widely accepted practices.

3. The final section presents the LCS advice developed by the SAGs (Clinical and Cognitive Outcomes, Fluid Biomarkers, Genetics, and Imaging) through evidence-based reviews of the literature. It should be noted that the LCS advice is subject to change in order to align with the Global Alzheimer's Platform (GAP).

References and links to supporting documentation are listed in Annex I.

1. Introduction

The European Prevention of Alzheimer's Dementia (EPAD) project is a secondary prevention adaptive trial aimed at evaluating potential "disease-modifying" drugs in Alzheimer's disease.[1] By modelling pre-dementia Alzheimer's disease (AD) and creating a mechanism for an adaptive double blind clinical trial, it is proposed that the EPAD Proof of Concept (PoC) trial will be able to study individuals who will benefit most from disease-modifying interventions, i.e., those with a high-risk profile and with clear evidence of disease-specific processes, who have not yet expressed clinical symptoms or present mild symptomatology.

1.1. Structure Of EPAD and WP1

The Innovative Medicines Initiative (IMI) EPAD project consists of three platforms: 1) EPAD Register, 2) EPAD Longitudinal Cohort Study (LCS), and 3) PoC Trial. Participants will be recruited into the EPAD Register (n = 24,000) primarily from pre-established parent cohorts accessed where possible using existing portals such as the IMI European Medical Information Framework (EMIF). The register will serve as a recruitment pool of participants who will then potentially be selected for the LCS. Participants eligible for the LCS (n = 6,000) will undergo baseline assessments and receive repeat assessments. While some participants will remain in the LCS, others will be selected for intervention, for which participants will be allocated to one treatment arm in the PoC (n = ~ 1,500) and will undergo the EPAD PoC protocol.

Eight interrelated work packages[2] (WPs) were formed in order to create the EPAD platforms. The EPAD delivery cluster, a core group of WPs (WPs 1 through 4 with input from WP8), is leading the development of the EPAD platforms. Within the delivery cluster, WP1 is tasked with providing scientific input for the development of the selection criteria and the protocol for data collection. WP1 is composed of three co-leads (Andrew Satlin, Eisai Inc.; Gary Romano, Janssen; Simon Lovestone, University of Oxford), project management support (David Ruvolo, University of Oxford; WP5), five Scientific Advisory Groups (SAGs), and the Clinical Compound Selection Committee (CCSC, lead: Andrew Satlin, Eisai Inc.). The five WP1 SAGs are the Clinical and Cognitive Outcomes (CCO-SAG, lead: Karen Ritchie, Institut National de la Santé et de la Recherche Médicale), Epidemiology (lead: Carol Brayne, University of Cambridge), Fluid Biomarkers (lead: Bruno Dubois, Hôpital de Salpêtrière), Genetics (lead: Julie Williams, Cardiff University), and Imaging (lead: Frederik Barkhof, Stichting VU-Vumc). The SAGs each have approximately six expert members chosen by the SAG leads, as well as external advisors and support staff.[3]

The primary outcome of the SAGs is to establish the scientific advice for the register, the LCS, and the PoC trial in order to recruit patients on a "risk spectrum" (defined in section 1.1). The register recommendations 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. Ultimately, the advice given for

the PoC trial is high-level expert advice agreed on by WP1 leads and regulatory authorities for use in the PoC trial, and will also reflect data that accrue in the LCS.

1.2. EPAD Risk Spectrum

As previously stated, the scientific advice is designed to recruit participants on a "risk spectrum," which is defined as individuals who have evidence of or are at risk for developing AD-dementia, but who are asymptomatic or mildly symptomatic though not demented.

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2. Recommendations for the EPAD Register

The purpose of this section is to present the recommendations for the EPAD register established by WP1 SAGs. All recommendations are based largely on expert opinion and the most widely accepted practices within the field. The SAGs framed their recommendations on minimizing screen failures[4] during the recruitment to the EPAD cohort, taking into account the heterogeneity between parent cohorts (PCs) and the fact that data may not be readily available or standardised. The recommendations were established through a series of teleconferences and face-to-face meetings between March and April of 2015, and these recommendations were later presented to the EPAD general assembly (May 20, 2015).[5]

The EPAD register will consist of a minimum of 24,000 participants who are at least 50 years of age and who have evidence of or are at risk for developing AD-pathology, but who are asymptomatic or mildly symptomatic though not demented and meet the following recommendations:

2.1. Clinical and Cognitive Outcomes SAG Recommendations

- The clinical endpoint SAG highly prefers requesting results from previous psychometric assessments, specifically any episodic-memory task, as this information would be used for cohort selection and for excluding AD dementia cases.[6]

With regard to the criteria for the register, given the very heterogeneous cognitive testing methods used within the EMIF cohorts, it was concluded that test-specific 'fingerprinting' would not be possible. The group suggested that, assuming there had been at least one episodic memory test given within age cohorts, Z-scores should be derived from this test for each individual, thus providing a normally distributed range of cognitive scores for each cohort in which individual participants could be placed in relation to others. This would allow the statistical work group to stipulate further criteria for inclusion in the cohort (e.g., selecting persons with age and education adjusted z-scores falling below the mean).

2.2. Epidemiological SAG Recommendations

- The Epidemiology SAG made no mandatory recommendations for the register, although demographic data is preferred.

Epidemiology is the newest addition to WP1 and recommendations for the register were not available at the time of the EPAD general assembly. In recent meetings, WP1 leads and SAG leads suggested that family history and standard group characteristics (e.g., age, education, medical history, etc.) are helpful for defining the EPAD register population; however, this information would not serve as criteria for the register.

2.3. Fluid Biomarkers SAG Recommendations

- The Fluid Biomarkers SAG made no mandatory recommendations for the register; Cerebrospinal fluid (CSF) data or samples should be requested if available,[7] as this information would be considered during selection into the cohort. The Biomarker SAG recognises that molecular fluid biomarkers will not be available for register selection purposes.

2.4. Genetics SAG Recommendations

- The genetics SAG state Apolipoprotein-E (APOE) status, DNA and genome-wide Single Nucleotide Polymorphisms (SNP) data should be requested where available, but not made mandatory for entry to the register.[8]

The Genetics SAG recommends that, where possible, polygenic scores (PS) be calculated as an exploratory basis on the 24,000-participant register. Genome-wide association studies (GWAS) data may not be available for all participants, but PS should be generated for those with data available. This can be achieved by submitting available GWAS data to the Genetics group or by liaising with said group for advice and information regarding its calculation.

Genetic variants associated with Alzheimer's disease (APP, PSEN1 and 2) are primarily observed in cases of early-onset AD and are rare in occurrence, and are excluded from EPAD where as other variants (i.e., TREM2, R47H) may be used as stratification factors. SNP data, including the risk variants derived from genome-wide association studies, should be requested where available.

2.5. Imaging SAG Recommendations

- The Imaging SAG highly prefers requesting hippocampal atrophy as measured by MRI, metabolic, and molecular imaging data,[9] as this information would be used for group stratification and ruling out unrelated pathology.

Structural imaging data is highly preferred for determining hippocampal atrophy. Atrophy will be calculated as age-corrected z-scores for hippocampal volume derived from comparison to a control group (e.g., parent cohort or secondary datasets – such as the Alzheimer's Disease

Neuroimaging Initiative, or ADNI). Tracing methods (manual, semi/fully-automated) will be employed to measure hippocampal volume.

Other data from structural imaging is important for setting criteria for the cohort, providing information needed to rule out unrelated pathology, visually assessing vascular loading (using Fazekas or ARWMC score), and determining amyloid angiopathy. Other data that should be accessed if available include molecular (Amyloid) and metabolic (FDG-PET, HMPAO-SPECT, ASL-MRI) imaging.

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3. Advice for the EPAD Longitudinal Cohort Study

The purpose of this section is to present the advice for the EPAD Longitudinal Cohort Study (LCS) established by WP1 SAGs. The cohort advice is based on reviewing the current literature, following widely accepted practices, and minimizing participant burden. The SAGs established the cohort advice through a series of teleconferences and face-to-face meetings between May and July of 2015.[10]

As previously stated, the LCS advice is subject to change in order to align with the Global Alzheimer's Platform (GAP) and feedback from regulatory authorities. In particular, the Imaging SAG may need to further develop guidelines and recommendations to be similar with protocols used in GAP. The Clinical and Cognitive Outcomes SAG may need to align clinical and cognitive measures (e.g., cognitive domains, outcome measures, etc.) with GAP. Details regarding specific alignment will occur as discussions between EPAD and GAP leadership begin in the upcoming months.

The LCS will consist of a minimum of 6,000 participants who will be selected according to the proposed criteria and will undergo the assessments described below.

3.1. General WP1 Recommendations

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 regulatory authority approved measures of clinical state. It is recommended to include these measures as part of the standard clinical assessment rather than the core clinical endpoints battery.

1. Clinical Dementia Rating Scale (CDR)

The CDR (Morris, 1993) is comprised of two separate semi-structured interviews one with the individual and another with a reliable collateral source (informant, i.e., partner, family

member or relative, friend, or any other closely related individual) conducted by a CDR certified clinician. During the interview, the clinician assesses the patient's current status in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) and rated accordingly using a 5-point scale (0 = normal, 0.5 = mild dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia)[11]. Outcome measures of the CDR are a Global CDR score (derived from an algorithm developed by the Knight ADCR), the CDR sum of boxes (CDR-sb, the sum of all six domains), and a CDR rating for each domain.

2. Mini-Mental Status Exam (MMSE)

The MMSE is a 30-item mental status questionnaire that assesses a patient's mental status (orientation, memory, attention, language, visualspatial abilities, and calculation). A total MMSE score is calculated by summing of all correct items out of a possible thirty points.

3.2. Clinical and Cognitive Outcomes SAG LCS Advice

- The Clinical and Cognitive Outcomes SAG recommends annual administration of the EPAD battery to all participants in the LCS.[12]

For the cohort and the trial instruments, it was decided to develop a single test battery covering multiple domains. The entire battery of tests should ideally be given annually to all members of the cohort. The results from these testing waves would provide normative data for the cohort for either the whole population or sub-groups. For the trials, the entire proposed neuropsychological examination should again be used with parallel versions being provided to permit retesting more than once per year. Based on the empirical findings from the LCS regarding the reliability of the specific measures and subtests in the ENE and their sensitivity to longitudinal change, and based on the presumed mechanism of action of individual interventions being tested in the PoC, specific subtests or composite score(s) will be selected for the determination of efficacy in the PoC trial.

From this very large panel of potential testing procedures (see white paper), SAG members discussed and compared the relative merits of different tests according to the following criteria:

- Available translations (given the number of countries and languages involved, it is acknowledged that there will be additional translation work for some tests at least at the administration instruction level)
- Good psychometric properties
    - Priority given to measures with high sensitivity rather than specificity, given that the battery is for signal detection and not diagnosis
- Alternative Forms (or ability to easily create fully alternative versions)
- Validated preferably by reference to longitudinal data in relation to either

  - Preclinical through prodromal populations
  - APOE +
  - Amyloid +
- Normative data available
- Limited (or well-defined) practice effects
- Where previously existing tests used, preference for non-proprietary material
- Suitable for non-specialist administration

From this discussion, a short-list of tests was determined by majority vote and a table was constructed permitting further comparison of their psychometric properties.[13]

On the basis of these further psychometric criteria, a final list of tests was selected which adequately covered all domains likely to be implicated, with 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. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) versions of several pre-existing tasks that were rated highly by the SAG were chosen for some domains, given that they were psychometrically equivalent and provided the additional benefit of having multiple parallel forms, which did not exist in the original tests (e.g. the Rey Figure).

The final cognitive domains and corresponding tests selected, arranged according to their proposed order of administration, are the following:

1. **<u>Reaction Time/Information Processing Speed/Conceptual Shifting/Selective Attention:</u>**

   a) Flanker (NIH EXAMINER/Toolbox)

   The Eriksen Flanker Task is a set of response inhibition tests used to assess the ability to suppress responses that are inappropriate in a particular context. The target is flanked by non-target stimuli which correspond either to the same directional response as the target (*congruent* flankers), to the opposite response (*incongruent* flankers), or to neither (*neutral* flankers). In the tests, a directional response (usually left or right) is assigned to a central target stimulus. Various forms of the task are used to measure information processing and selective attention.

   b) Coding (RBANS)

   The Coding Test is a measure of brief, focused visual attention, visual scanning and processing speed. The participant must rapidly draw simple designs associated with a specific number. Accuracy and speed are recorded.

2. **<u>Verbal Episodic Memory:</u>**

a) List Learning (RBANS)

List Learning measures rote verbal memory for unrelated information. The participant hears a list of 10 unrelated words and must repeat the words back to the examiner. The word list is presented to the participant a total of four times, evaluating ability to learn verbal information after repeated exposure. After a delay with intervening tasks, the participant will recall the list over three further trials.

b) Story Memory (RBANS)

The task measures memory for conceptually related verbal information. The participant hears a story that is two sentences in length and must repeat the story back to the examiner. The participant hears the story two times; therefore, the subtest also measures verbal learning. Following a delay with intervening tasks, the story is recalled to assess long-term verbal memory encoding and retrieval.

3. Visuospatial analysis

a) Figure Copy (RBANS)

The Figure Copy task requires the copying of a complex geometric design from a model, implicating visuospatial reasoning, attention to visual details, motor programming, and, to a lesser degree, organization and fine-motor ability. After a delay, the figure is redrawn from memory without prior warning to measure long-term free recall for conceptually-related visuospatial information and incidental memory (i.e., memory for information that was encoded without specific effort to do so).

b) Line Orientation (RBANS)

The Line Orientation task assesses ability to correctly identify the angle and spatial orientation of lines in two-dimensions. The participant is presented with 13 lines fanning out in different directions, which they are required to differentiate according to angle.

4. Language:

a) Picture Naming (RBANS)

The Picture Naming task measures confrontation naming skills. This is a direct assessment of expressive language skills often impaired in global and specific types of aphasia, specifically dysnomia. The participant is shown 10 drawings of common objects and asked to name each one. The drawings are simple line drawings to avoid any perceptual confusion that more complex drawings may create.

b) Semantic Fluency (RBANS)

The Semantic Fluency task measures the participant's ability to retrieve and express words using a semantic prompt. This is a direct assessment of expressive language skills often impaired in global and expressive aphasia. The participant is asked to say as many words as possible associated with a specific category of objects within a fixed time limit.

5. **Working Memory:**

a) Digit Span (RBANS)

The Digit Span subtest is a measure of auditory registration and brief focused attention. The participant listens to a series of digits read out by the examiner at one per second (e.g., 2–9) and is asked to repeat the digits in reverse order.

b) Dot Counting (NIH Examiner)

This verbal working memory task is presented on a computer screen as a mixed array of green circles, blue circles and blue squares, and the participant is instructed to count all of the blue circles on the screen and remember the final total. The examiner then switches the display to a different mixed array of green circles, blue circles and blue squares. The participant is instructed to count the blue circles in the new display. The number of different displays presented to the participant in each trial increases from two to seven over six trials. After counting the blue circles on all of the displays presented within a trial, the participant recalls the total number of blue circles in each of the different displays in the order in which they were presented.

6. **Allocentric Space: Four Mountains Task (Cambridge Cognitive Neurosciences)**

The test assesses linkage between the episodic and spatial functions of the hippocampus, which permits representation of spatial information in an allocentric form and hence encoding of the context in which events occur. Computer-generated landscapes comprised of four hills (of varying shape and size) surrounded by a distant semicircular mountain range are presented with a sample image for 10 seconds following which the participant is immediately presented with four alternative images, one of which (the target image) shows the same topography as the sample image, seen from a novel viewpoint, from which they must identify the target image by pressing a key. Non-spatial features (lighting, vegetation, weather conditions) of both target and foil landscapes are varied between presentation and testing, such that transient local features of the image cannot be relied on to solve the task.

7. **Paired-Associate Learning: Name-Face Pairs (UCSF)**

The Face Name Associative Memory task is a behavioral version of a cross-modal associative memory test based on an fMRI task that pairs pictures of unfamiliar faces with common first names. The test requires the participant to learn 16 unfamiliar face-name pairs and 16 face-occupation pairs displayed for 8 seconds. The test consists of

an initial learning phase, immediate cued recall, delayed cued recall, facial recognition, and a multiple choice recognition trial.

8. **<u>Navigation in Egocentric Space: Virtual Reality Supermarket Trolley (University College London)</u>**

   This test, which is sensitive to deterioration in the precuneus, retrosplenial cortex and entorhinal connections measures egocentric spatial orientation (as opposed to allocentric space) through presentation of 14 video vignettes in an ecological virtual supermarket from a first person perspective. A route through the supermarket in which the participant is behind the trolley involves a series of 90° turns, and at the end the participant is required to point in the direction of the entry.

It is recommended by the SAG that each component task should have four alternative forms for retesting across the trial period and a training trial. A global test score should be derived from the battery as well as subtest scores and qualitative observations. Where possible tests will provide both a primary measure (correct responses) and secondary measures (latency or information processing times). The battery should be developed such that it is "modulable"; that is, individual components may be selected out corresponding to specific drug targets if necessary. It is desirable, however, that the EPAD cohort participants complete the entire battery at each wave, as this will in parallel produce normative data. A measure of subjective memory was not included, as presently available data has often been based on poor study design, is inconsistent and has little discriminative value. The Mini Mental Status Exam (MMSE; or similar screening or staging instruments) is not included in the core clinical endpoints battery, as it is not considered to be a psychometric test. Its utility (along with global indicators such as Clinical Dementia Rating scale) is principally as a clinical descriptor and should therefore, if included in EPAD, be part of the participant clinical characteristics (see below). It is considered unsuitable as an outcome, as shown in the recent Cochrane report.[14]

The tests selected are all suited for tablet administration and data collection, and the SAG recommends this. Almost all tests are already available in the languages of the clinical centers; additional translations, notably of instructions, should be undertaken only by a professional group, preferably one likely to be acceptable to regulatory bodies such as TransPerfect.

<u>A library of articles</u> (in progress) relating to the psychometric characteristics and validation of the tests both short-listed and selected has been constituted in the EPAD CogSAG site work space, for further reference but in particular as evidence for regulatory bodies. Following the link and entering the test name will provide you with an article relating to the test.

Other Clinical Outcomes

In addition to the cognitive examination, other clinical endpoints were recommended following a review of currently available measures and examination of their previous performance in both epidemiological studies and clinical trials. The principal secondary clinical outcomes recommended by the SAG are depression, anxiety, sleep disturbances, and

everyday functioning. Depression, anxiety and sleep changes have been associated with both early biomarker change and cognitive dysfunction. Changes in everyday activities in pre-clinical AD are detectable only using scales specifically designed for this purpose – the more widely used activities of daily living (ADL) and instrumental activities of daily living (IADL) questionnaires are unlikely to be sensitive to very early changes.

The selection criteria adopted by the SAG in their evaluation measures were the following:

- Known neurophysiological links to cognition
- Sensitive to at least mild cognitive impairment (MCI)
- Good repeat-test reliability
- Validated in European countries
- Dimensional or otherwise able to demonstrate change over time

2. Mini-Mental Status Exam (MMSE)

The MMSE is a 30-item mental status questionnaire that assesses a patient's mental status (orientation, memory, attention, language, visualspatial abilities, and calculation). A total MMSE score is calculated by summing of all correct items out of a possible thirty points.

Although as noted before, the SAG does not recommend the including the MMSE as a part of the core cognitive battery. The SAG suggests using it as a standard measure that is regularly used in studies and recognized by regulatory authorities. It is recommended to include the MMSE as part of the standard clinical assessment.

3. Depression

The **Geriatric Depression Scale** (GDS) is a 30-item self-report assessment used to identify depressive symptomatology in the elderly. The GDS questions are answered "yes" or "no". One point is assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0-9 as "normal", 10-19 as "mildly depressed", and 20-30 as "severely depressed". A diagnosis of clinical depression should not be based on GDS results alone. The test has well-established reliability and validity with 92% sensitivity and 89% specificity when evaluated against diagnostic criteria. Although a shorter version (15 items) has been validated, the longer version is more likely to have a normal distribution—hence better adapted for use as a dimensional scale—without reliance on theoretical clinical cut-off points. The larger range of items also permits a finer analysis by symptom cluster and not just overall score.

4. Anxiety

The **State-Trait Anxiety Inventory** (STAI) is a psychological inventory based on a 4-point Likert Scale consisting of 40 self-report questions. The STAI measures separately both state anxiety (fear, nervousness, discomfort and autonomic nervous system arousal induced by specific situations) and trait anxiety (chronic feelings of stress, worry, discomfort experienced

on a day-to-day basis). Each type of anxiety has its own scale of 20 different questions on a score range from 20 to 80, with higher scores correlating with greater anxiety.

5. Sleep

The Pittsburgh Sleep Quality Index is a self-rated questionnaire that assesses sleep quality and disturbances over a one-month time interval. Nineteen items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and sleep-related daytime dysfunction. The sum of scores for the seven components gives a global score. The index has adequate internal consistency and high retest reliability, with a diagnostic discriminability of 89.6% sensitivity and 86.5% specificity for good and poor sleepers.

6. Everyday Functioning

a) **The Amsterdam Instrumental Activities of Daily Living Questionnaire** is an informant-report checklist aimed at detecting early activities of daily living changes associated with pre-clinical stage dementia. The test has high internal consistency and retest reliability with construct validity established by comparing estimated trait levels with clinical and demographic measures.

b) **Body Worn Actigraphy** monitoring provides objective measurement of rest-activity periods or cycles and their variability across time. The method has been shown to reveal more valid measures of activity level than proxy assessment and subjective report, although it is limited to short time samples. Actigraphs may be worn at different positions (limbs, waist), but most practical for consideration here is wristwatch-like devices with an accelerometer that detects physical motion above or below a set threshold, which is recorded and stored in digital form. Analysis algorithms have been applied to this raw time-stamped data to predict basic activity such as time at rest or active and nighttime behaviors related to sleep. The actigraph is usually worn for a period of 2 to 3 weeks to sample daily activity levels. Consideration of a particular device depends on the basic outcome measures desired and the feature set that a device may have to best meet the desired outcome measures (e.g., user friendly form factor, being waterproof, power or charging requirements, data transfer protocol, etc.)

   EPAD should consider the use of actigraphs as early phase testing where outcome measures would be relevant to EPAD or as a mechanism for further development of this technology. It is recognized that this is a rapidly changing field with emergent technologies and that EPAD should be open to utilization of early phase and development tests utilizing pervasive computing and peripheral devices. This technology might measure a range of phenotypes and outcomes of relevance to EPAD.

3.3. Genetics SAG LCS Advice

- 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.[15]

Current literature indicates that rare variants of strong genetic effect (APP, PSEN1&2) are too rare in the population to justify testing in the EPAD cohorts. In addition, most of these rare mutations are observed in those with early-onset AD and are unlikely therefore to be included in the EPAD cohort.

The Genetics SAG recommends enriching by a polygenic score for the LCS where available as an exploratory measure, and ideally all 6,000 would be genotyped for the SNPs contributing to polygenic score. A custom chip could be produced, including all AD polygenic variants, at an approximate cost of £40.

Currently, the SAG is producing polygenic scores for specific functional pathways, such as immunity and cholesterol transportation. That data will be available to inform selection for further clinical trials and could also be of value when testing drugs associated with specific disease pathways.

The Genetics group has discussed the configuration of the genetic profiles chosen for individuals selected for clinical trials. It is recommended to enrich for high PS, but not to choose samples exclusively on this basis. It is possible that those with high biological risk and those that have a more varied aetiology could respond differently. Therefore all participants selected should have known polygenic scores, but it is recommended that the samples include high AD risk and those of variable genetic risk. This data should be used as exploratory information to support future analyses.

The SAG recognises that the polygenic score is likely to be most useful in combination with other variables indicating early stage AD, such as cognitive symptoms and/or biomarkers, including plaque deposition.

NOTE For the advice provided by the Imaging and Biomarkers SAG, participants will be selected into the LCS by molecular marker (i.e., CSF). The SAGs will provide additional evidence and rationale (from review of the literature, discussions with WP1 leadership) to establish specific criteria for cut-offs and thresholds.

3.4. Fluid Biomarkers SAG LCS Advice

- The Fluid Biomarkers SAG recommends inclusion of CSF measures of AD pathology (Aβ, 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.

The advice takes into account the importance of standardisation and harmonisation and the work being conducted to ensure cross-laboratory consistency in these assays across Europe. The availability of different assays for these measures was also taken into account. The SAG recommends the use of a single analytical laboratory where possible and the adoption of protocols for sample collection, storage and CSF assays as developed by leading European laboratories in this field.

Other exploratory markers in CSF

The SAG notes that other assays (Neurogranin and VILIP-1 in CSF) are being developed and are unlikely to be further validated during the lifetime of EPAD. For this reason the SAG strongly recommends collection and storage of CSF for exploratory studies of these assays and other analyses.

Exploratory markers in blood

The SAG strongly recommends the collection and storage of plasma and serum together with consideration of collection and storage of cells and material for RNA using widely approved protocols. The group notes that the iSTAART PIA led by Sid O'Bryant has done much to standardise these protocols. Using similar protocols to collect materials EPAD could be used productively to validate putative blood biomarkers and to further develop novel markers of considerable potential utility in EPAD and future clinical trials. These biomarkers include, but are not limited to:

- **Araclon blood based Aβ measures:** Araclon is a partner in EPAD and claims an assay indicative of brain pathology load. This assay requires an independent protocol for blood collection but we recommend using the EPAD platform to further validate these measures. If they are validated in the LCS, then there is considerable potential to utilise these assays in the PoC. It is strongly recommended to incorporate these measures on an exploratory level.

- **Acute phase and inflammatory proteins:** Evidence suggests other blood-based biomarkers derived from proteomic studies and largely, but not exclusively, proteins of inflammation. Some protein sets yield strong predictions of conversion from pre-dementia to dementia and others a weak prediction of brain pathology. The Biomarkers SAG recommends using EPAD samples to further validate these and other blood biomarkers. This is a moderate recommendation on an exploratory level.

3.5.Imaging SAG LCS Advice

- 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 year two.

Imaging SAG Cohort Advice Background

For the LCS, the Imaging SAG established evidence-based advice by reviewing studies with an emphasis on secondary prevention of AD, defined from an imaging perspective as amyloid pathology in the brain without necessary signs of accompanying neurodegeneration. The usefulness of the imaging data for the subsequent PoC studies, both in terms of inclusion and as potential outcomes, was also considered.

Starting from studies of mild cognitive impairment (MCI) and progression to clinical AD, the Group focused on pertinent literature on earlier disease stages. This literature covered subjective memory complaints (SMC), subjective cognitive impairment (SCI) and healthy controls (HC). The Imaging SAG based the LCS advice largely on longitudinal data, but cross-sectional data was also considered, especially when stratified for amyloid status and APOE4.

Three imaging modalities – *molecular*, *structural and functional* – were considered since they confer complementary information regarding disease susceptibility, pathology and impairment. The Imaging SAG also factored in patient burden, implementation and costs, while avoiding redundancies between imaging measures and non-imaging procedures. The group believes that novel (MRI) techniques that are non-invasive and rapidly acquired provide a wealth of data for the future.

Imaging SAG Cohort Advice

For each imaging modality, the recommendations and frequency of assessment for the EPAD LCS are described under the bullet point at the beginning of this section and summarized in the table below. Information regarding specific deliberations and technical recommendations is presented subsequently; supplementary evidence and review can be found on the teamwork site.[16]

Table 1: Imaging Modalities and Frequency for the EPAD LCS

No.	Modality	Baseline	Year 1	Year 2	Year 3	Year 4
1.	Molecular	**Amyloid-PET**		*Amyloid-PET (subset)*		

2.	Structural	**MRI** *(subset DTI)*	**MRI**	**MRI** *(subset DTI)*	**MRI**	**MRI**
3.	Functional	*ASL/rsFMRI/early-frame PET (subsets)*		*ASL/rsFMRI/early-frame PET (subsets)*		

Recommendation 1: Molecular Imaging - Amyloid-PET at screening for all participants

Though the Imaging SAG finds Tau-tracers potentially very interesting, currently the field is too immature to implement them in the EPAD cohort. This, however, may change by the time participants enter the PoC trials (even when drugs target amyloid rather than tau). Similarly, the field of microglia imaging, using so-called TSPO tracers, is immature, and at the moment, the candidate drugs for PoC trials do not focus on this target. The limited sensitivity of MR spectroscopy means this is not an adequate substitute for molecular imaging with PET tracers.

Only the evidence for Amyloid-PET was compelling enough for inclusion in the LCS, as it conveyed important prognostic information regarding cognitive decline and conversion to AD. Amyloid-PET seems more objective, (regionally) sensitive and fine-grained than CSF measures of amyloid and therefore is complementary rather than competitive. Sensitivity to changes seems to be present if quantification is done properly, but it requires dynamic scanning, with early-frame data also providing flow information.

For the implementation of Amyloid-PET imaging in the LCS, the Imaging SAG makes the following recommendations:

- Include at least 10-20 minutes, depending on the tracer used, during the plateau phase of tracer binding, which typically takes place around 90 -110 minutes post-injection.

- Perform additional early dynamic scanning at 0 - 30 minutes p.i., which can be separated by a coffee break or MRI, to allow full quantification of the binding potential (BP) and calculation of blood flow images. This should be achievable in 20-30 sites.

- Consider repeating Amyloid-PET in participants with normal or borderline amyloid positivity after two years.

- The outcome measure from the static phase is a standardised uptake value (SUVR) in a composite cortical ROI, using a composite reference ROI of WM and cerebellum. In the subset with early-phase imaging, the BP in the cortex can be determined additionally.

- Careful site selection, phantom scanning and quantification procedures are required.

- Given the burden of Amyloid-PET, some type of enrichment strategy should be enforced to prevent the testing of too many SMC/SCI participants with negative Amyloid-PET scans. Beyond screening using (historic) CSF-Amyloid levels, this could entail selecting participants who are older, APOE4 positive or have a family history of AD. In order to detect very early phases of the Amyloid deposition, we envisage enrolling three strata of participants using both a definitive threshold for positivity (SUVR>1.4) determined from AD, as well as a threshold for intermediate probability (SUVR of 1.08). **NOTE** These recommendations regarding to cut-off scores are preliminary and subject to revision.

Recommendation 2: Structural Imaging - Structural MRI in all participants at baseline and then at yearly intervals

Though CT can provide useful information to rule out surgical pathology and can even be used for visual analysis of hippocampal atrophy, MRI is strongly favoured over CT because it provides lower radiation exposure and the possibility to determine vascular pathology while allowing for quantification of grey matter structures such as the hippocampus and other AD signature regions.

MRI is also much better suited to a longitudinal setting (i.e., measurements at yearly intervals), with subtle changes over time detected in AD sensitive regions starting during the preclinical phase (with adequate statistical power), which predict future cognitive decline and onset of dementia. Atrophy rates can also serve as an outcome in PoC trials, for which the LCS would provide run-in data, or be used to enrich the included sample. Yearly MRI provides a fair balance between patient burden and determination of (non-linear) trajectories of atrophy. Diffusion tensor imaging (DTI) measures Brownian motion along brain fibres and holds promise for detecting early changes in tissue quality even longitudinally.

For the implementation of Structural MRI in the LCS, the Imaging SAG makes the following recommendations:

- Scanning should include anatomic 3D-T1 for segmentation and grey-matter quantification purposes, as well as FLAIR/T2/T2* to determine vascular co-morbidity and microbleeds, which can be completed in less than 30 minutes. DTI should be acquired in subsets, adding an additional 5 to 10 minutes.

- Preferred outcome measures are hippocampal and whole brain volume as well as vascular burden (WM lesions, infarcts, lacunes, microbleeds and superficial siderosis).

- Exploratory outcomes including cortical thickness in AD-signature regions and deep GM volumes.

- For DTI, focus on fractional anisotropy (FA) of the temporal lobe and diffusion kurtosis (when using multi b-value DTI) in subgroups. DTI can also map network alterations.

- ADNI-like protocols and quality control are mandatory to ascertain precision in measuring change, preferably done using direct longitudinal measurement techniques (rather than segmentation only). Standardisation is needed for DTI (b-factor encoding schemes and distortion).

Recommendation 3: Functional Imaging - ASL and resting-state fMRI in a sizeable subset at baseline and year two

Probably the best-studied modality is FDG-PET, with prognostic metabolic information predictive of cognitive decline in AD, MCI and even normal aging. However, given the strong rationale to employ Amyloid-PET, it is felt that there would be major difficulties incorporating another fluorinated PET tracer, as this would require an additional visit and radiation exposure.

Arterial Spin Labelling (ASL) is an emerging MRI technique that offers non-invasive regional cerebral blood-flow quantification. ASL is becoming more widely available and can be added to the structural MRI protocol with little cost and time constraint (5-7 minutes). Early-frame Amyloid-PET also conveys flow information and could be examined in selected sites performing dynamic scanning.

Resting-state fMRI (rsfMRI) measures spontaneous oscillations in local blood oxygenation related to brain activity and can be acquired in 5-8 minutes of scanning. Though little is known about its sensitivity to change, reproducibility is good in a multicentre setting. Resting-state fMRI provides data similar to MEG, which is not widely available. Data on using (longitudinal) EEG across multiple centres is lacking, and the Imaging SAG does not advise this to be implemented, though the SAG lacks in-depth expertise.

For the implementation of ASL and rsfMRI in subsets of the LCS, the Imaging SAG makes the following recommendations:

- ASL can be added to the structural MRI protocol with little cost and time constraint (5-7 minutes). Resting-state fMRI can be acquired in an additional 5-8 minutes of scanning.

- Preferred outcome measures are global and parietal CBF for ASL and changes within the default-mode network (DMN) and its relation with hippocampal activity for rsfMRI.

- Exploratory outcomes might include bolus arrival time (when using multi-delay ASL) and network analysis for rsfMRI.

- Standardization is needed for ASL (sequences and minimizing physiological fluctuations) and rsfMRI (temporal and spatial resolution and distortion).

ANNEXES

Annex I. Notes

[1] EPAD Description of work: https://epadpm.teamwork.com/files/1121596?v=1

[2] The EPAD WPs are as follows:

WP	Name	Description*
1	Scientific Challenges	Responsible for all scientific input and advice for the EPAD register, cohort, and PoC trial.
2	Statistical Engine Room	Informatics group tasked with trial design and disease modelling for the LCS and PoC.
3	Parent Cohorts and Register	Oversee the collaboration with parent cohorts and development of the EPAD register
4	EPAD Cohort and PoC	Coordinates the LCS and develops master protocols for LCS and PoC
5	Project Management	Ensure professional management of trade-offs between scope, time, cost and quality to ensure progress and successful completion of the project
6	Dissemination	Reports on all EPAD activities with stakeholders, participants, and the general public
7	Business Model and Sustainability	Create a business plan for sustainability beyond the time frame of the project and will configure a pre-competitive space for IPR handling and business workflows to enable the consideration of compounds coming from different companies within EPAD, including provisions for conflict resolution, prioritisation and other business matters.
8	Ethical, Legal, and Social Implications	Address ethical issues raised throughout EPAD and key issues - consent process, disclosure of test results, implications of biomarker testing, data security and confidentiality, risk management of adaptive trial design

[3] WP1 SAG Composition and Overview: https://epadpm.teamwork.com/files/1744426

[4] LCS Exclusion Criteria (from: "EPAD LCS Protocol Draft 2.0 26 08 2015.docx"):

- Participants who fulfill diagnostic criteria for any type of dementia (e.g. NINCDS-ADRDA for AD; Lund Criteria for FTD, McKeith Criteria for DLBD, NINCDS-AIREN Criteria for Vascular Dementia)
- Carriers of a PSEN1, PSEN2 or APP mutation associated with Autosomal Dominant AD
- Presence of any neurological, psychiatric or medical conditions associated with a long-term risk of significant cognitive impairment or dementia including but not limited to pre-manifest Huntington's disease, multiple sclerosis, Parkinson's disease, Down syndrome, active alcohol/drug abuse or major psychiatric disorders including schizophrenia, schizoaffective or bipolar disorder
- Any cancer or history of cancer in the preceding 5 years
- Any conditions affecting safe engagement in potential clinical trials, e.g. symptomatic cardiovascular disease (including re-vascularization procedures within the previous year), severe renal or hepatic failure, severe loss of vision, hearing or communicative ability, conditions preventing co-operation as judged by the study physician
- Any contraindications for MRI/PET scan or Lumbar Puncture
- Any evidence of intracranial pathology that may affect cognition including but not limited to brain tumors (benign or malignant), AV malformations, stroke, intracranial bleeding, mass lesion or NPH. Subjects with a MRI scan demonstrating minimal white matter changes and up to 1-2 lacunar infarcts judged to be clinically insignificant are allowed
- Participation in any other clinical trial of an interventional agent in the last 30 days

[5] WP1 SAG Recommendations for the EPAD Register: https://epadpm.teamwork.com/files/1603386

[6] CCO-SAG London Meeting, May 2015: https://epadpm.teamwork.com/files/1677079

[7] Biomarkers Recommendations: https://epadpm.teamwork.com/files/1645138

[8] Genetics Recommendations: https://epadpm.teamwork.com/files/1639161

[9] Imaging Recommendations: https://epadpm.teamwork.com/files/1603

[10] WP1 SAG Lead Meeting July 15, 2015 – Cohort Advice Preliminary Drafts: SAG Meeting Slides

[11] CDR Administration and Scoring Overview: http://knightadrc.wustl.edu/cdr/aboutcdr.htm

[12] CCO-SAG White Paper: https://epadpm.teamwork.com/files/1795943

[13] CCO-SAG Psychometric Properties Table: https://epadpm.teamwork.com/files/1797808

[14] Cochrane Report: Cochrane Report

[15] Genetics SAG Documentation:
- Genetics SAG Recommendations: https://epadpm.teamwork.com/files/1797810
- Genetics SAG Review: https://epadpm.teamwork.com/files/1797812

- Genetics Sag Review Supporting Tables: https://epadpm.teamwork.com/files/1797811
- Genetics SAG Slides: https://epadpm.teamwork.com/files/1797813

[16] Imaging SAG Documentation:

- Imaging SAG Review Draft: https://epadpm.teamwork.com/files/1795942
- Imaging SAG Literature Overview: https://epadpm.teamwork.com/files/1797857
- Imaging SAG Literature Review: https://epadpm.teamwork.com/files/1797856