The European Prevention of Alzheimer’s Dementia (EPAD) and Amyloid Imaging for Prevention of Alzheimer’s Dementia (AMYPAD) Projects: Cohort Readiness for the Adaptive Clinical Trial Platform


www.ep-ad.org
I have recently sat on paid advisory boards for Merck, Pfizer, Eisai, Actinogen, Kyowa, Roche and Eli Lilly
The EPAD Consortium

Academia

SMEs

Patient Organisation

Other industry

EFPIA

AMYPAD
UCL
GE
Piramal

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The EPAD Project Structure

The EPAD Delivery Cluster

EXISTING KNOWLEDGE

- Clinical
- Genetic
- Epidemiology

NEW EPAD-DERIVED KNOWLEDGE

- Cognitive
- Imaging
- Biomarker

Risks for AD

Expression of AD

Optimal patient profile
Optimal PoC Outcomes
Optimal Interventions

WP 1

WP 4/8

Trials Master Protocol

Go/No-Go on intermediate biomarker phenotype then cognition

WP 5-8: Supporting Work Packages
The EPAD Flow

**EPAD trial “machine”**

- **LOW** probability, based on risk factors, disease evidence, symptoms
- **HIGH** probability, based on risk factors, disease evidence, symptoms

**Enrichment Journey**

- Parent Cohorts
- Virtual register
- Research Participants (RPs)
- Identified by fingerprinting

- Longitudinal Cohort
- Study-RPs
- phenotype & monitored

- Alzheimer's Probability Spectrum

- Proof of Concept Study
- Single Sponsor
- Multiple Treatment arms

- Placebo arm
- Shared across study

- Study arm 1
- Study arm 2
- Study arm 3

- Continuous LCS recruitment

- Adaptive design

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Current potential search fields available in Parent Cohorts

General and demographics
- **Diagnosis of cognitive disorder**
- Diagnosis (date)
- **Age**
- **Gender**

Risk factors and biomarkers
- **Apoe4 alleles**
- **First degree relative has AD**
- CSF amyloid (baseline and change)
- CSF p-tau (baseline and change)
- CSF t-tau (baseline and change)
- CSF (date)
- Average MTA-score (and collection date)

Cognitive tests
- MMSE score (and collection date)
- MMSE (decline per year)
- Delayed recall z-score
- Delayed recall (decline per year)
- Immediate recall z-score
- Immediate recall (decline per year)

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Objectives of EPAD LCS
- Readiness for the EPAD PoC Trial
- Disease Modelling
  - Improved simulations and stratification
- Run-in data for PoC
- Risk stratification

The balance of the EPAD LCS needs to accommodate each of these, though in the above hierarchy
EPAD LCS: inclusion criteria

- Basic inclusion criteria
  - Age ≥ 50 years of age
  - Participants able to read and write, ≥ 7 years of education
  - Do not satisfy clinical criteria for any type of dementia
  - Not known to carry a PSEN1, PSEN2 or APP mutation
  - Do not have any neurological, mental or medical condition associated with a risk of cognitive impairment or limiting psychometric testing
  - Do not have cancer or a history of cancer in the preceding 5 years
  - Are willing to participate in the EPAD PoC Trial subject to further informed consent
Cognitive Outcomes - Primary

- **RBANS** - Repeatable Battery for the Assessment of Neuropsychological Status
  - Verbal Episodic Memory: List Learning & Story Memory
  - Visual Episodic Memory: Figure recall
  - Visuospatial/Constructional: Figure Copy & Line Orientation
  - Language: Picture Naming
  - Attention/Executive Functioning: Semantic Fluency, Digit Span, Coding

Cognitive Outcomes

- **Dot Counting** (working memory, NIH Examiner, secondary)
- **Flanker** (choice reaction time and set-shifting, NIH Examiner, secondary)
- **Name/Face Pairs** (paired associate learning, University of California, San Francisco, secondary)
- **Four Mountains Task** (allocentric space, Cambridge Cognitive Neurosciences, exploratory)
- **Virtual Reality Supermarket Trolley** (navigation in egocentric space, University College London, exploratory)
Biomarker Outcomes

- **Secondary outcomes**
  - **CSF biomarker outcomes: Aβ, t-tau, p-tau** – inclusion of Roche Diagnostic as a new EPAD partner
  - Blood, urine, saliva for genomics and assessment of emerging biomarkers
  - **Neuroimaging outcomes**
    - **Structural MRI**
      - Cortical thickness, deep grey matter volumes
      - Fractional anisotropy (FA) of temporal lobe, diffusion kurtosis (multi b-value DTI), network alterations
    - **Functional MRI**
      - Global & parietal CBF
      - Changes within the default-mode network & relation with hippocampal activity (rsfMRI)
      - Bolus arrival time (multi-delay ASL)
      - Network analysis (rsfMRI)
    - **PET Amyloid Imaging (AMYPAD-IMI2)**
Other Assessments

- Other clinical outcomes
  - Depression: 30-item Geriatric Depression Scale (GDS)
  - Anxiety: State-Trait Anxiety Inventory (STAI)
  - Sleep: Pittsburgh Sleep Quality Index
  - Everyday functioning: Amsterdam Instrumental Activities of Daily Living Questionnaire

- Socio-demographic and lifestyle factors, family history of AD/dementia in first degree relatives, medical history, comorbidity, medication use, BMI, waist-hip ratio, blood pressure, CDR, MMSE.

- Dementia diagnosed by the participant’s physician
- Physical examination
- APOE genotype
EPAD: LCS design

1. Once recruitment is completed, at any given time there should be approx. 6,000 research participants in the EPAD LCS and approx. 1,500 in the EPAD PoC, hence the need to replenish each as participants are lost through attrition.
AMYPAD Prognostic and Natural History Study overview

Parent Cohorts

EPAD LCS

Amypad PNHS Selection and Feasibility Committee

EPAD timeline

Month 0
Baseline (EPAD LCS)

Month 6
Visit 2 (EPAD LCS)

Month 18
Follow-up (EPAD LCS)

Month 60

EPAD LCS Screening n~3500

AMYPAD PNHS

n~3,200

Baseline Scan Dynamic + Static

Baseline scan Static

Algorithm

n~1,600

Follow-up scan

Follow-up scan No scan

Algorithm

End of study (Dec 2021)

AMYPAD timeline

4th quarter 2017

Baseline PNHS (EPAD LCS Visit 2 - 90d + 30d)

Follow-up PNHS (12-24m after baseline)

n≈3,200

Amypad PNHS Selection and Feasibility Committee

Algorithm

Month 0

Month 6

Month 18

Month 60

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EPAD LCS Participant Recruitment

EPAD LCS Participant Recruitment: Actual May 16 to Aug 17 + Predicted

N=378 on 1st November ‘17 and 9 open sites
Aims of analysis

- **Readiness**
  - What proportion of current LCS research participants are amyloid positive on CSF?

- **Selection**
  - Which factors are associated with amyloid positivity in the current research participants?
  - From parent cohorts what is the predictive value of key variables that could be used for selection?
<table>
<thead>
<tr>
<th></th>
<th>Whole Population (n=374)</th>
<th>Full analytical dataset (n=232)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean[SD])</td>
<td>66.4 [6.3]</td>
<td>66.2[6.1]</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (%M)</td>
<td>49%</td>
<td>48%</td>
<td>NS</td>
</tr>
<tr>
<td>Years of Education (mean [SD])</td>
<td>14.3 [3.8]</td>
<td>14.2[3.6]</td>
<td>NS</td>
</tr>
<tr>
<td>Family History +</td>
<td>74%</td>
<td>74.4 %</td>
<td>NS</td>
</tr>
<tr>
<td>CDR (% CDR=0.5)</td>
<td>13%</td>
<td>15.4%</td>
<td>NS</td>
</tr>
<tr>
<td>MTA Score &gt;= 1</td>
<td>14%</td>
<td>13.5 %</td>
<td>NS</td>
</tr>
<tr>
<td>ApoEe4 + (n=248)</td>
<td>NA</td>
<td>e4/e4  5%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>e4/ -  41%</td>
<td></td>
</tr>
<tr>
<td>CSF Ab42 (mean[SD])</td>
<td>NA</td>
<td>1296 pg/ml (401 pg/ml)</td>
<td>NA</td>
</tr>
<tr>
<td>CSF Tau (mean [SD])</td>
<td>NA</td>
<td>225.3 pg/ml (99.7 pg/ml)</td>
<td>NA</td>
</tr>
<tr>
<td>CSF pTau (mean [SD])</td>
<td>NA</td>
<td>20 pg/ml (10.7 pg/ml)</td>
<td>NA</td>
</tr>
<tr>
<td>% Amyloid Positive (CSF Ab &gt;1,000 pg/ml)</td>
<td>NA</td>
<td>28%</td>
<td>NA</td>
</tr>
</tbody>
</table>
What proportion of current LCS research participants are amyloid positive on CSF?

<table>
<thead>
<tr>
<th>Amyloid status summary</th>
<th>CDR 0</th>
<th>CDR 0.5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid positive (CSF $\alpha_1$-42 &lt; 1000 pg/ml)</td>
<td>47</td>
<td>18</td>
<td>65</td>
</tr>
<tr>
<td>Amyloid grey zone (CSF 1000 ≤ $\alpha_1$-42 ≤ 1200 pg/ml)</td>
<td>23</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Amyloid negative (CSF $\alpha_1$-42 &gt; 1200 pg/ml)</td>
<td>130</td>
<td>12</td>
<td>142</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>32</td>
<td>232</td>
</tr>
</tbody>
</table>

CDR 0.5 = 56% Positive  
CDR 0 = 23.5% Positive

Proportion of CDR 0.5 due to increase substantially from 13% (whole sample) because of new sites patient access and PrePAD Velocity being approved.

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Which factors are associated with amyloid positivity in the current research participants?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male)</td>
<td>1.39</td>
<td>0.68 – 2.90</td>
<td>0.36</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>1.08</td>
<td>1.01 – 1.15</td>
<td>0.01</td>
</tr>
<tr>
<td>ApoEe4 carrier</td>
<td>2.6</td>
<td>1.27 – 5.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Average MTA Score</td>
<td>1.56</td>
<td>0.66 – 3.63</td>
<td>0.29</td>
</tr>
<tr>
<td>Family History of AD in FDR</td>
<td>3.1</td>
<td>1.29 – 8.01</td>
<td>0.01</td>
</tr>
<tr>
<td>CDR Score</td>
<td>13.49</td>
<td>0.41 – 29.14</td>
<td>0.24</td>
</tr>
<tr>
<td>RBANS Total</td>
<td>0.97</td>
<td>0.94 – 0.99</td>
<td>0.09</td>
</tr>
</tbody>
</table>
From parent cohorts what is the predictive value of key variables that could be used for selection?

<table>
<thead>
<tr>
<th></th>
<th>ApoEe4 -</th>
<th>ApoEe4 +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Negative</td>
<td>96</td>
<td>61</td>
</tr>
<tr>
<td>Amyloid Positive</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>NPV = 96/119 (80.6%)</td>
<td>PPV = 38/99 (38%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Family History -</th>
<th>Family History +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Negative</td>
<td>44</td>
<td>123</td>
</tr>
<tr>
<td>Amyloid Positive</td>
<td>12</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>NPV =44/56 (78.6%)</td>
<td>PPV = 54/177 (30.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CDR 0</th>
<th>CDR 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Negative</td>
<td>149</td>
<td>17</td>
</tr>
<tr>
<td>Amyloid Positive</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>NPV =149/197 (75.6%)</td>
<td>PPV = 17/34 (50%)</td>
</tr>
</tbody>
</table>
From parent cohorts what is the predictive value of key variables that could be used for selection?

- If $\text{CDR} = 0.5$ AND $\text{ApoEe4+} = 11/15$ amyloid positive (73.3%)
- If $\text{CDR} = 0.5$ AND $\text{ApoEe4-} = 6/18$ amyloid positive (33.3%)
- If $\text{CDR} = 0$ AND $\text{ApoEe4+} = 26/83$ amyloid positive (31.3%)
- If $\text{CDR} = 0$ AND $\text{ApoEe4-} = 17/100$ amyloid positive (17%)

**Conclusion:**
- If can gain access to ApoE status and select on this can increase by 23.3% yield of amyloid positivity in $\text{CDR}=0.5$
**Research Access and Data Releases**

Data Access: Relatively straightforward (training and version control)
Participant Access: Most likely at a site/regional level

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>V500.0</td>
<td>V500.1</td>
<td>V500.2</td>
<td>V500.3</td>
<td>V500.4</td>
</tr>
<tr>
<td>1000</td>
<td>V1000.0</td>
<td>V1000.1</td>
<td>V1000.2</td>
<td>V1000.3</td>
<td>V1000.4</td>
</tr>
<tr>
<td>3000</td>
<td>V3000.0</td>
<td>V3000.1</td>
<td>V3000.2</td>
<td>V3000.3</td>
<td>V3000.4</td>
</tr>
</tbody>
</table>

*Increasing Value for Novelty Sample Access*

*Exception is genetic analysis*
Acknowledgments

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