The Neuronet Sessions: European Prevention of Alzheimer’s Dementia
Alzheimer’s Europe Conference: October 2019

Prof Craig Ritchie
Co-coordinator EPAD
Prof of Psychiatry of Ageing: University of Edinburgh
Chair: Scottish Dementia Research Consortium
Director: Brain Health Scotland

@craig_ritchie68
The Background and on-going need for EPAD

The project structure and Neuronet
  – Participants
  – Cohort
  – Trial
  – Academy

The EPAD Assets and their realisation from 2020 for global progress
  – The 5 Component Model

Data access and releases
Presentation Content

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- Data access and releases
Complexity

- The Brain is Complex
- Alzheimer’s Disease is Complicated
- People are complex
- Time to embrace complexity
The world (until now) has only seen Neurodegenerative Brain Disease through the ‘peep hole’ of ‘Dementia’
The world (until now) has only seen Neurodegenerative Brain Disease through the ‘peep hole’ of ‘Dementia’
Drug development

Unsuccessful investigational drugs for Alzheimer's disease 1998–2018

Number of Alzheimer’s disease drugs no longer under development

4 total approved medicines including Aricept in 1996
Causation of Failure

- Restrictive Costs
- Screen Failure
- Non-adaptive design

Less Conservatism

- Disease Stage

- Insensitive Outcomes

Accelerated or absent Phase 2
EPAD

Disease Stage

- Accelerated or absent Phase 2
- Restrictive Costs
- Screen Failure
- Non-adaptable design

Sensitive Outcomes

Solutions to Failure

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- Data access and releases
The EPAD consortium
The EPAD consortium

- Public/private consortium funded (€64M) by the Innovative Medicines Initiative (IMI) designed to increase successful development treatments secondary prevention AD in pre-dementia patients.

- Thirty-nine partners including academia, pharmaceutical industry (European Federation of Pharmaceutical Industries and Associations (EFPIA)).

- Five years of initial IMI funding; project began 2015. Sustainability planning beyond 2019 in progress. 6-months no-cost extension until June 2020.

- Project has 8 work packages grouped in 2 clusters: delivery and support.
**Cognitive Outcomes**

**Primary: RBANS**
- 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

**Secondary:**
- Dot Counting
- Flanker
- Name/Face Pairs
- Four Mountains Task
- Virtual Reality Supermarket Trolley

**Biomarker Outcomes**
- CSF biomarker outcomes: Aβ, t-tau, p-tau Blood, urine, saliva for genomics and assessment of emerging biomarkers
- Neuroimaging outcomes
  - Structural MRI
  - Functional MRI
  - PET Amyloid Imaging (AMYPAD)

**Other**
- Risk Factors: including genomics (NeuroX)
- Lifestyle
- Physical comorbidities (including TBI)
- Demographics
- Mood, anxiety, sleep, apathy
### EPAD Coordinators

- **Serge Van der Geyten**  
  Janssen Pharmaceutica NV
- **Craig Ritchie**  
  University of Edinburgh

### Work Packages of EPAD

<table>
<thead>
<tr>
<th>Work package name</th>
<th>Role in the EPAD study</th>
<th>Work package leads</th>
</tr>
</thead>
</table>
| WP1 Scientific Challenges | Science behind EPAD  
Finding suitable participants for EPAD | Jose Luis Molinuevo  
Scott Berry  
Adrian Mander  
Shobha Dhadda  
Philip Hougaard |
| WP2 Statistical/Methodology Engine | Mathematics around how to measure change in brain health | Gary Romano  
Pieter Jelle Visser |
| WP3 Parent Cohorts (register) | Running the trial visits and seeing EPAD participants | Gerald Luscan  
Craig Ritchie  
Miia Kivi pelto |
| WP4 EPAD Cohort and EPAD Trials | Managing the whole EPAD project | Carlos Diaz  
Serge Van der Geyten |
| WP5 Project Management | Communicating about the EPAD work | Jean Georges  
Sean Knox |
| WP6 Dissemination | EPAD funding and how to sustain the longevity of the study | Saira Ramasastry  
Jose Luis Molinuevo  
Serge Van der Geyten |
| WP7 Business Model and Sustainability | Ethical & social issues around Alzheimer's disease | Richard Milne  
Edo Richard  
Carol Brayne |
| WP8 Ethical, Legal and Social implications | | |

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**SLIDE 17**
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Data access and releases
Participants
Aim of the Participant panel

- **Provide feedback** on good and bad elements of study experience and recommendations for improvements
- Ensure that participants are represented in **decision making** which may affect them such as sub-studies or study logistics
- **Review documents** related to the study aimed at participants such as Information Sheets or Recruitment flyers
- Work with the EPAD team to **communicate about the study** at national and international conferences
Participant panels so far across the EPAD study

<table>
<thead>
<tr>
<th>Country</th>
<th>Panel progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotland</td>
<td>Panel meets regularly</td>
</tr>
<tr>
<td>Nordics</td>
<td>Not yet – planning stage</td>
</tr>
<tr>
<td>England</td>
<td>Not yet – planning stage</td>
</tr>
<tr>
<td>Switzerland and Italy</td>
<td>Not yet – planning stage</td>
</tr>
<tr>
<td>France</td>
<td>Panel meets regularly</td>
</tr>
<tr>
<td>Spain</td>
<td>Panel meets regularly</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Setting up the panel</td>
</tr>
</tbody>
</table>

Upcoming study sites

Updated 31st May 2019
The Background and on-going need for EPAD

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Data access and releases
Longitudinal Cohort Study participating countries/sites

- UEDIN, Edinburgh (Scotland)
- BBRC, Barcelona (Spain)
- CHUT, Toulouse (France)
- VUmc, Amsterdam (The Netherlands)
- CITA, San Sebastian (Spain)
- KI, Stockholm (Sweden)
- CHU Montpellier (France)
- UNIGE, Geneva (Switzerland)
- CHUN, Nantes (France)
- CHRU, Lille (France)
- Tayside (Scotland)
- Paris Nord (France)
- Paris La Pitié Salpêtrière (France)
- WLMHT, London (UK)
- GM:CRN, Manchester (UK)
- NHS Grampian (Scotland)
- NHS Glasgow (Scotland)
- NHS Bristol (UK)
- Brescia (Italy)
- Cambridge (UK)
- CHUV, Lausanne (Switzerland)
- Perugia (Italy)
- Aeginition Hospital Athens (Greece)
- Gothenburg (Sweden)

40 Trial Delivery Centres activated
11 countries involved

Updated 10th October 2019
Data collected in the EPAD Longitudinal Cohort Study

**Neuropsychological Examination**
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) includes:
  - 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
- Dot counting
- Flanker
- Four Mountains Task
- Supermarket TrolleyVirtual Reality
- Favourites (Delay, Learning & Recognition)

**Biomarkers**
- CSF biomarkers: beta-amyloid, t-tau, p-tau, Polygenic Scores
- Neuroimaging parameters (MRI): hippocampal and whole brain volume; vascular burden (WML, infarcts, lacunes, microbleeds, superficial siderosis)
- Blood samples
- Urine samples
- Saliva samples

**Risk factors**
- APOE genotype
- Family history of AD/dementia in first degree relatives
- Sociodemographic factors: age, sex, education, marital status, ethnicity
- BMI
- Medical history: cardiovascular and cerebrovascular conditions, chronic respiratory conditions, chronic systemic inflammatory conditions, depression, cancer, general anaesthesia after the age of 50 years, head injury
- Lifestyle factors: smoking, drug abuse, alcohol consumption, diet, physical activity, life events, self-rated health and fitness

**Other clinical outcomes**
- The Geriatric Depression Scale
- The State-Trait Anxiety Inventory (STAI)
- The Pittsburgh Sleep Quality Index
- The Amsterdam Instrumental Activities of Daily Living Questionnaire
- MMSE (Mini Mental State Examination)
- CDR (Clinical Dementia Rating)
Recruitment Status 24 Oct 2019

- Open sites
- Projected sites
- Withdrawal/screen fail
- Participants screened
- Active Participants

#Sites
#Research Participants

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Recruitment Status Per Site
24 Oct 2019
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Data access and releases
PoC protocol

**Master PoC protocol**

- Description of common framework of the PoC trial and minimum inclusion and exclusion criteria for all interventions

**Appendix to the master protocol**

- Specifically for each intervention cohort. Will define the specific information and additional trial elements and inclusion/exclusion criteria
EPAD adaptive trial design

Longitudinal Cohort Study

Proof-of-Concept Trial

Drug study A
- 3 participants
- 1 participant
- Active treatment
- Placebo (shared across all of the drug studies)

Drug study B
- 3 participants
- 1 participant
- Active treatment
- Placebo (shared across all of the drug studies)

Drug study C
- 3 participants
- 1 participant
- Active treatment
- Placebo (shared across all of the drug studies)

Equal randomisation into concurrent drug studies
PoC Platform Set-up (Behind the Curtain)

- **ASC**
  - Appendix Steering Committee
  - Manages the Appendix

- **DSMB**
  - Data Safety Monitoring Board
  - Responsible for Appendix safety

- **IDMC**
  - Independent Data Monitoring Committee
  - Responsible for Evolutionary Analyses

- **PSC**
  - PoC Steering Committee
  - Manages the Platform

- **TDCs**
  - Trial Delivery Centres

- **Sponsor**

- **IQVIA**
  - 3rd Party Vendor Contracting and Management
  - Statistics Oversight
  - IWRS
  - Clinical Trial Supplies
  - CSF Lab
  - Central Lab
  - Cognitive tests
  - MRI Central Reader
  - ECG Central Reader

- **Regulatory & Study Initiation Activities**
  - IMP Management with Intervention Owner
  - Site Management & Compliance (Monitoring)

- **Study & Project Management**
  - Manage Enrollment
  - Study Close Out Activities

- **Safety Reporting Management**
- **Statistics Activities**

- **Trial Database**

- **TMF**
  - Data Management

- **Assist Sponsor with QA Activities (management of CAPA)**

Dotted line applies at Appendix level
The EU Registry /LCS are funded through a grant from Innovative Medicines Initiative (IMI) up till June 2020.
Presentation Content

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EPAD Academy - Mission

- To help create the next generation of AD researchers and thought leaders, by creating and facilitating opportunities for junior researchers’ career advancement.

- To create fair and efficient procedures for EPAD and non-EPAD research teams to access EPAD data, samples and research participants with the objective of deepening the understanding of AD onset and progression, and the factors contributing to underlying processes.

- To support the EPAD academic output in terms of scientific publications, participation in conferences and development of guidelines and studies, and to maximise their visibility and impact.
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Key EPAD Assets

EPAD Register
- 30,000 research participants over 50 years old

EPAD Longitudinal Cohort Study
- Up and running in 25 TDCs
- And more than 1,900 research participants enrolled

Proof of Concept Framework
- Established
- Ready to start, FPI by January 2020

EPAD Academy
- Established
- 60+ Fellows

Research Participant Panels
- Established
- Acting as a voice for the research participants in EPAD
**The EPAD Counsel**

Representative group of funders, component leadership, independent experts and lay members

**Purpose:** provide a forum for the EPAD components to collaborate with each other

---

Each of the 5 components have completely independent governance and management structures and different sources of funding

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**EPAD TDC Network**

- **Database**
  - Aridhia
  - Paid for by Philanthropy from June 2021

- **TDC Fees**
  - Cap at 2,500 Participants
  - To June 2021 paid for by EFPIA
  - From June 2021 – sites/countries find own funds to maintain their cohort

**EPAD Longitudinal Cohort Study**

**EPAD l’Academie**

**EPAD Registers**

**EPAD PoC Platform Trial**

---

**The LCS binds the TDC network therefore it is necessary to maintain the LCS post IMI**

**How:** LCS protocol; TDC contracts; vendor contracts

**Benefits:** maintain GCP/high quality; ensure consistency across the TDCs; readiness cohort; disease modelling; attractive to non-EPAD studies/sponsors.

**Vendors & Management**

100% EFPIA Funded

Ensures the quality of TDC network through the ‘main’ project – the LCS

- IQVIA
- MedAvante
- IXICO
- Edinburgh Sponsor and Management team

**BioResource (Edinburgh)**

- Paid for by Philanthropy from June 2021

---

**Structure and Function**

- Led from Toulouse
- Communications
- Scientific Networks
- Early Career Researchers
- Data access and monitoring of research outputs.
- General Assembly
- Self-funded

**Link to PoC**

- Main source from 2021 of recruitment to EPAD PoC

**Local, Regional & National**

- Overseen from a ‘WP3’ board of all national leads
- EPAD Advisory Minimum Dataset
- Self funded
- Clinic-based recruitment
- Data linked to Aridhia for recruitment oversight
- XX% PoC Recruitment funding to site
- XX% PoC Recruitment funding to Edinburgh
- Exemplars SBHR/DPUK2 and Germany
- May support recruitment for non-EPAD studies

---

**Structure**

- Edinburgh Sponsor and Management team
- Uses EPAD TDC Network (non-exclusivity)
- Recruits from EPAD LCS and then EPAD Register
- Trial platform established in 2019
- CCSC process operational 2018
- Funding model from Intervention Owners to vendors, TDCs and sponsor/CI office in place.
The Five Component (Asset) Model

- EPAD Trial Delivery Network
- EPAD Register
- EPAD Cohort
- EPAD Trial Platform

- BioBank
- Bolt on Studies
- Data Access
- Participants’ Panel
The Background and on-going need for EPAD

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Data access and releases
EPAD LCS Data Management Delivery Team

IQVIA
- Joseph Milne
- Siva Kumar
- Martin Dvořák
- IQVIA CRAs
- TDCs
- MedAvante team

WP2 UCAM
- Brian Tom Delivery Leader
- James Howlett

Aridhia
- Harry Peaker
- Bert Overduin
- Aridhia IT team

Bio-resource
- Jean Manson
- Fiona Scott
- WTCRF lab
- UGOT lab
- Roche DM

IXICO
- Mauro Sousa
- IXICO DM Team
- UEDIN & VUmc radiologists

ENE data & CI’s Office
- TabCAT @ UCSF
- Sammy Danso
- Judi Syson Delivery PM
- Craig Ritchie
- Graciela Muniz

Planning, Team Work & Delivery
What is EPAD RAP & What is WizeHive?

EPAD Research Access Process

http://ep-ad.org/erap/
How do you access EPAC LCS Data?

http://ep-ad.org

www.ep-ad.org

Simple online application

Direct data access

Data in workspace

Publish and share results

Step 1: WizeHive Login
How do you access EPAC LCS Data?

http://ep-ad.org

www.ep-ad.org

Simple online application

Direct data access

Data in workspace

Publish and share results

Step 2:
Research Access Application
How do you access EPAC LCS Data?

http://ep-ad.org

www.ep-ad.org → Simple online application → Direct data access → Data in workspace → Publish and share results

Fast Track

Partner – no approval required
How do you access EPAC LCS Data?

http://ep-ad.org

www.ep-ad.org

Simple online application

Direct data access

Data in workspace

Publish and share results

Fast Track

Partner – no approval required
Data Releases:

- **V500.0**  Embargoed Release: 18/5/19  Open Data Access: 18/11/19
- **V1500.0**  Embargoed Release: 28/11/19  Open Data Access: 28/5/20
- **V500.1**  Embargoed Release: December 2019  Open Data Access: June 2020
## Scientific publications

(All publications available here: [http://ep-ad.org/about/publications/](http://ep-ad.org/about/publications/))

<table>
<thead>
<tr>
<th>Authors</th>
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<tbody>
<tr>
<td>CW Ritchie et al.</td>
<td>09/12/2015</td>
<td>Development of interventions for the secondary prevention of Alzheimer’s dementia: the European Prevention of Alzheimer’s Dementia (EPAD) project</td>
<td>The Lancet Psychiatry</td>
</tr>
<tr>
<td>JL Molinuevo et al.</td>
<td>14/03/2016</td>
<td>Ethical challenges in preclinical Alzheimer’s disease observational studies and trials: results of the Barcelona summit</td>
<td>Alzheimer’s and Dementia</td>
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<td>M Mortamais et al.</td>
<td>01/10/2016</td>
<td>Detecting cognitive changes in preclinical Alzheimer’s disease: A review of its feasibility</td>
<td>Alzheimer’s and Dementia</td>
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<td>Recommended cognitive outcomes in pre-clinical Alzheimer’s disease: consensus statement from the European Prevention of Alzheimer’s Dementia (EPAD) Project</td>
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<td>S. Bemelmans et al.</td>
<td>10/11/2016</td>
<td>Psychological, behavioural and social effects of disclosing Alzheimer’s Disease biomarkers to research participants – a systematic review</td>
<td>Alzheimer’s Research &amp; Therapy</td>
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<tr>
<td>R. Milne et al.</td>
<td>22/02/2017</td>
<td>Ethical issues in the development of readiness cohorts in Alzheimer’s disease research</td>
<td>The Journal of Prevention of Alzheimer’s Disease</td>
</tr>
<tr>
<td>PJ Visser et al.</td>
<td>13/06/2017</td>
<td>Brain Amyloid Pathology and Cognitive Function. Alzheimer Disease Without Dementia?</td>
<td>JAVA</td>
</tr>
<tr>
<td>S Saunders et al.</td>
<td>13/12/2017</td>
<td>Evolution and future directions for the concept of mild cognitive impairment</td>
<td>International Psychogeriatrics</td>
</tr>
<tr>
<td>R Milne et al.</td>
<td>20/02/2018</td>
<td>Perspectives on Communicating Biomarker-Based Assessments of Alzheimer’s Disease to Cognitively Healthy Individuals</td>
<td>Journal of Alzheimer’s Disease</td>
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<tr>
<td>JL Molinuevo et al.</td>
<td>13/03/2018</td>
<td>The Rationale Behind the New Alzheimer’s Disease Conceptualization: Lessons Learned During the Last Decades</td>
<td>Journal of Alzheimer’s Disease</td>
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<td>28/03/2018</td>
<td>European Prevention of Alzheimer's Dementia Registry: Recruitment and prescreening approach for a longitudinal cohort and prevention trials</td>
<td>Alzheimer's &amp; Dementia</td>
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<tr>
<td>R Milne et al.</td>
<td>16/04/2018</td>
<td>At, with and beyond risk: expectations of living with the possibility of future dementia</td>
<td>Sociology of Health &amp; Illness</td>
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<td>E Bunnik et al.</td>
<td>28/08/2018</td>
<td>On the personal utility of Alzheimer's disease-related biomarker testing in the research context</td>
<td>Journal of Medical Ethics</td>
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<tr>
<td>M ten Kate et al.</td>
<td>30/10/2018</td>
<td>Secondary prevention of Alzheimer's dementia: neuroimaging contributions</td>
<td>Alzheimer's Research &amp; Therapy</td>
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<tr>
<td>S Gregory et al.</td>
<td>01/11/2018</td>
<td>Research participants as collaborators: Background, experience and policies from the PREVENT Dementia and EPAD programmes</td>
<td>Dementia</td>
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<td>A Solomon et al.</td>
<td>27/12/2018</td>
<td>European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol</td>
<td>BMJ Open</td>
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<td>M Smedinga et al.</td>
<td>12/12/2018</td>
<td>Ethical Arguments Concerning the Use of Alzheimer's Disease Biomarkers in Individuals with No or Mild Cognitive Impairment: A Systematic Review and Framework for Discussion</td>
<td>Journal of Alzheimer's Disease</td>
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<tr>
<td>Ramusino et al.</td>
<td>15/07/2019</td>
<td>Medial temporal lobe atrophy and posterior atrophy scales normative values</td>
<td>NeuroImage: Clinical</td>
</tr>
<tr>
<td>Archetti et al</td>
<td>23/07/2019</td>
<td>Multi-study validation of data-driven disease progression models to characterize evolution of biomarkers in Alzheimer's disease</td>
<td>NeuroImage: Clinical</td>
</tr>
</tbody>
</table>
Global fight against AD today: continuum of collaboration
Neuronet is in the cool club.......
Thank you!

Gracias

Merci

Grazie

Danke

Dank u

Tack
Acknowledgements

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115736, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.