

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

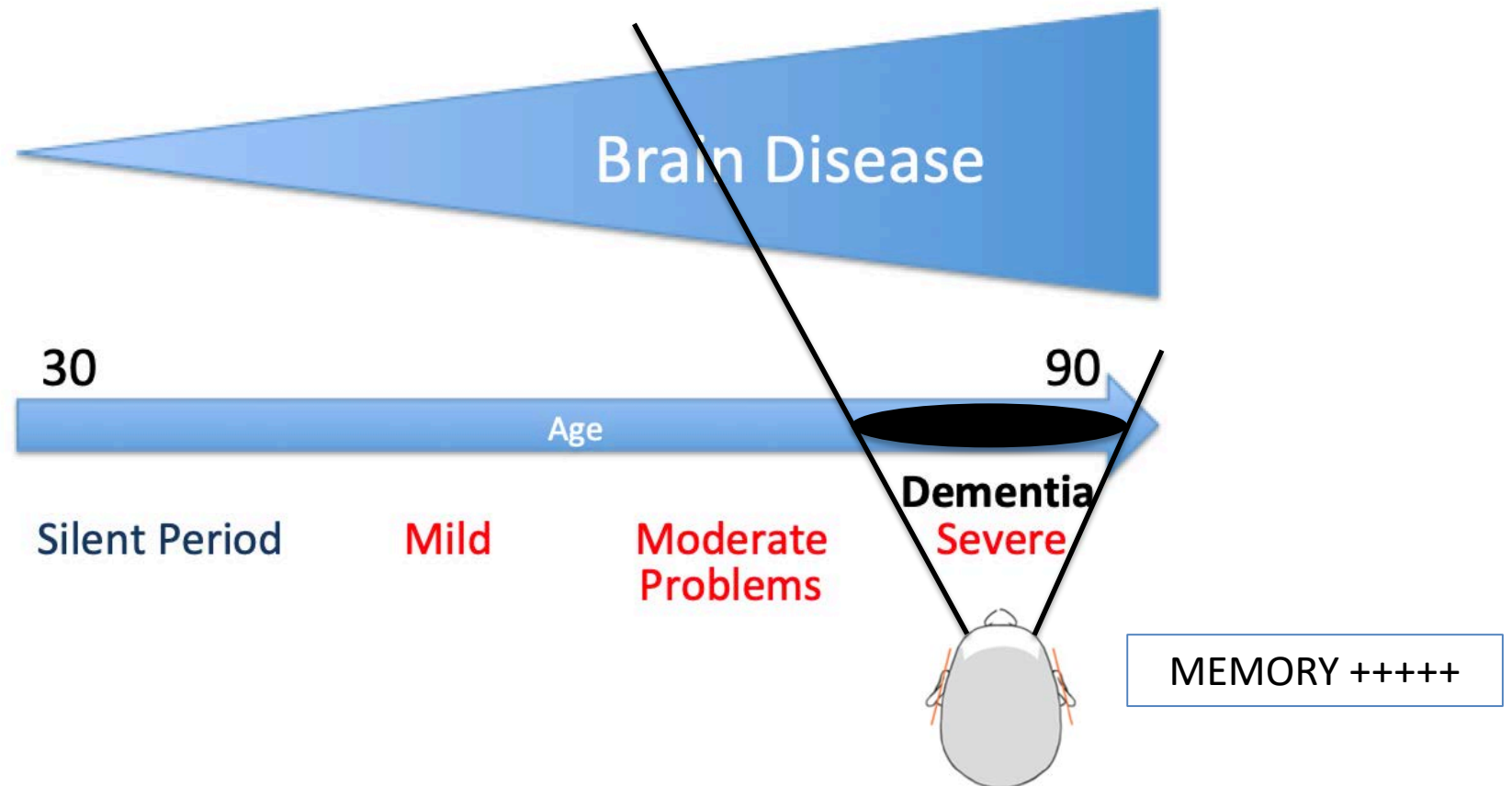
- The Background and on-going need for EPAD
- The project structure and Neuronet
 - Participants
 - Cohort
 - Trial
 - Academy
- The EPAD Assets and their realisation from 2020 for global progress
 - The 5 Component Model
- Data access and releases

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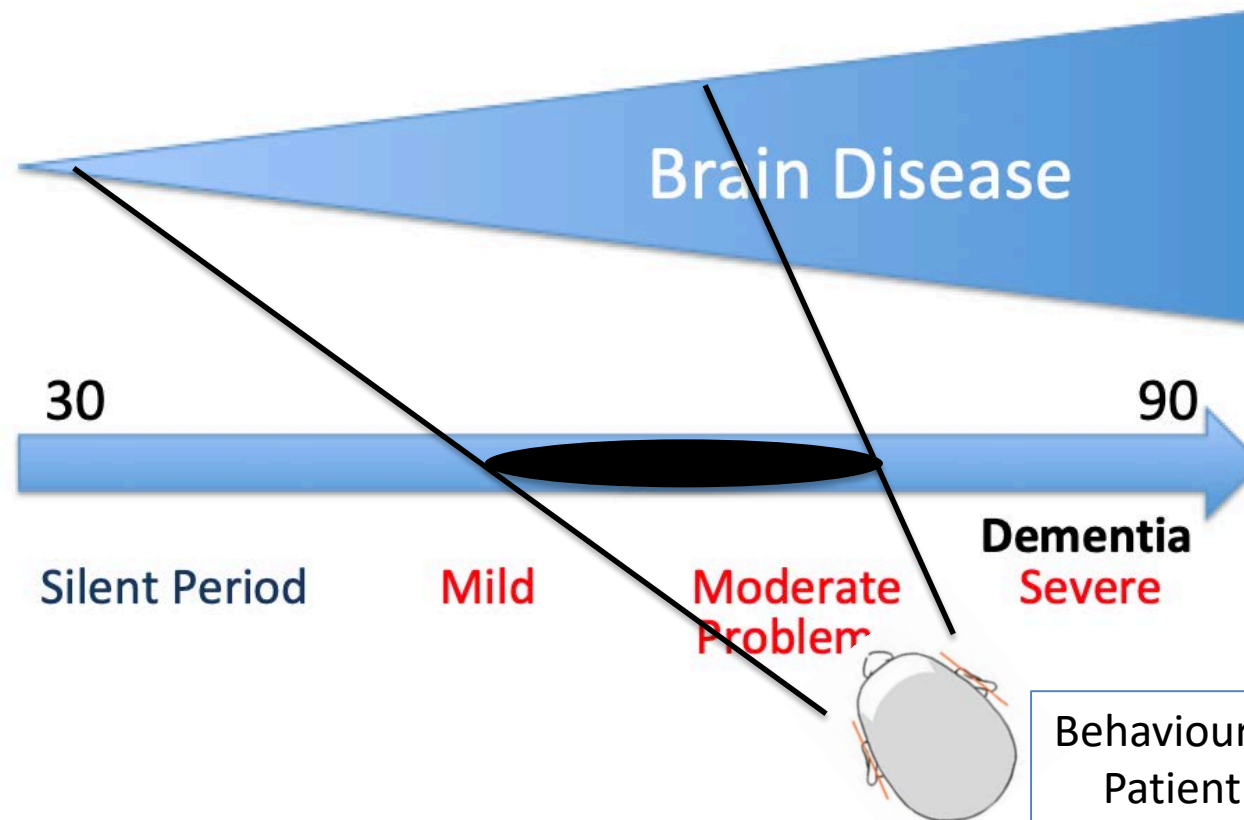
- The Brain is Complex
- Alzheimer's Disease is Complicated
- People are complex
- Time to embrace complexity



The world (until now) has only seen Neurodegenerative Brain Disease through the 'peep hole' of 'Dementia'

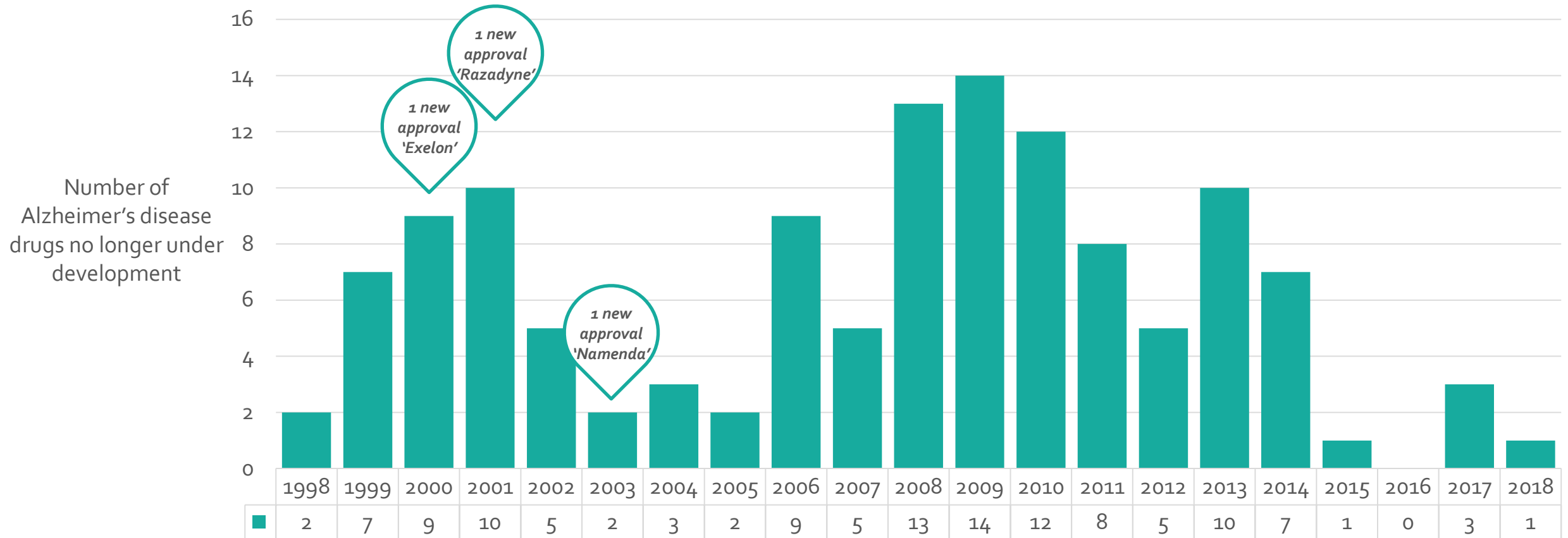


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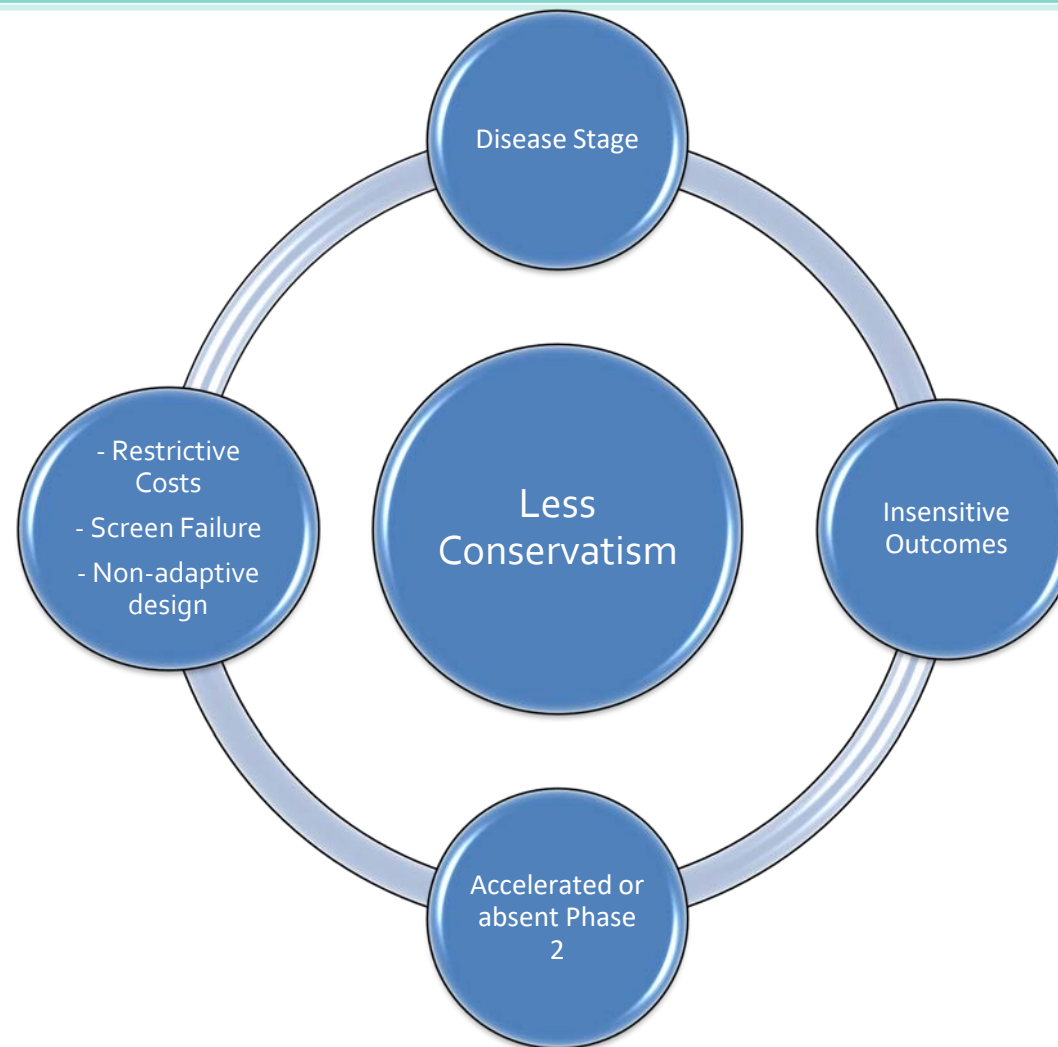
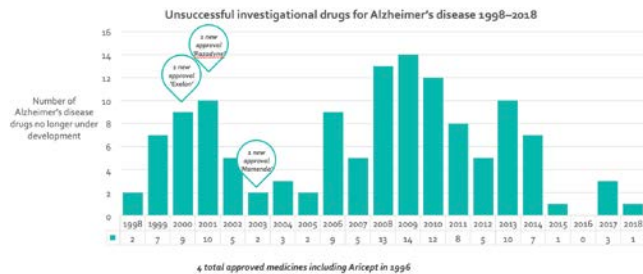
Behavioural, Other Cognitive &
Patient Related Outcomes
BIOMARKERS

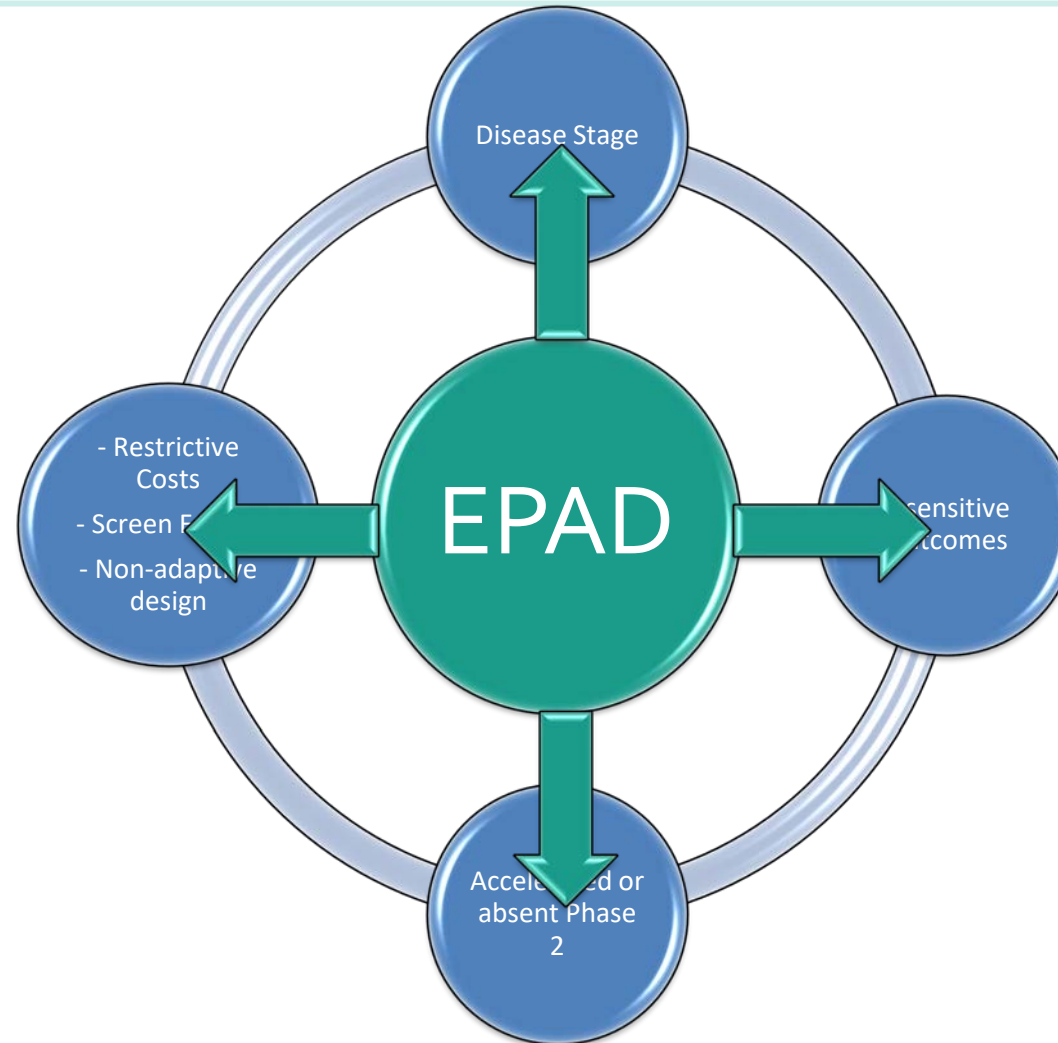
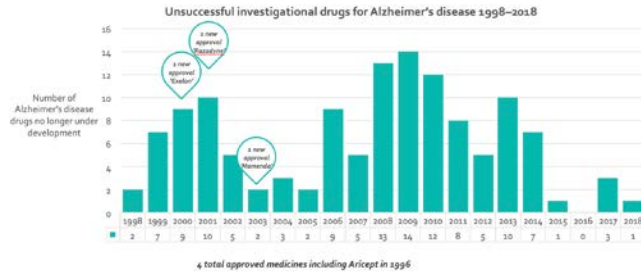
Unsuccessful investigational drugs for Alzheimer's disease 1998–2018



4 total approved medicines including Aricept in 1996

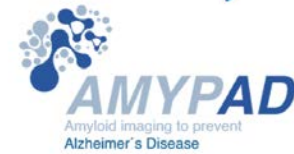
Causation of Failure





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The EPAD consortium

Academia



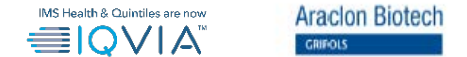
SMEs



Patient Organisation



Other industry



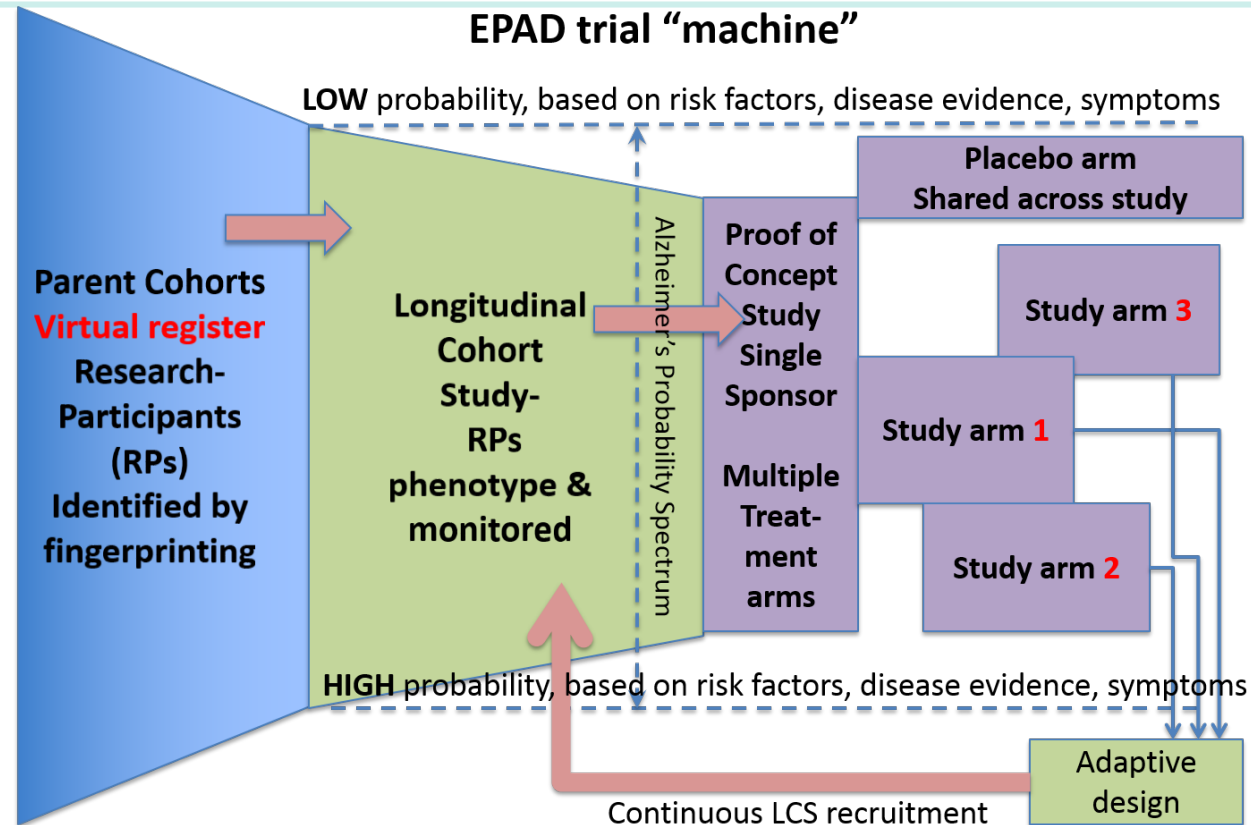
EFPIA



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: A β , 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

Open access Protocol

BMJ Open European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol

Alina Solomon,^{1,2,3} Mila Kivipelto,^{1,2,3} José Luis Molinuevo,⁴ Brian Tom,⁵ Craig W Ritchie,⁶ the EPAD Consortium

Work packages of EPAD

EPAD Coordinators



Serge Van der Geyten
Janssen Pharmaceutica NV



Craig Ritchie
University of Edinburgh

Work package name

WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8
Scientific Challenges	Statistical/ Methodology Engine	Parent Cohorts (register)	EPAD Cohort and EPAD Trials	Project Management	Dissemination	Business Model and Sustainability	Ethical, Legal and Social implications

Role in the EPAD study

Science behind EPAD	Mathematics around how to measure change in brain health	Finding suitable participants for EPAD	Running the trial visits and seeing EPAD participants	Managing the whole EPAD project	Communicating about the EPAD work	EPAD funding and how to sustain the longevity of the study	Ethical & social issues around Alzheimer's disease
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Work package leads

Jose Luis Molinuevo Gary Romano	Scott Berry Adrian Mander Shobha Dhadda Philip Hougaard	Gerald Luscan Pieter Jelle Visser	Lisa Ford Craig Ritchie Miia Kivipelto	Carlos Diaz Serge Van der Geyten	Jean Georges Sean Knox	Saira Ramasastry Jose Luis Molinuevo Serge Van der Geyten	Richard Milne Edo Richard Carol Brayne
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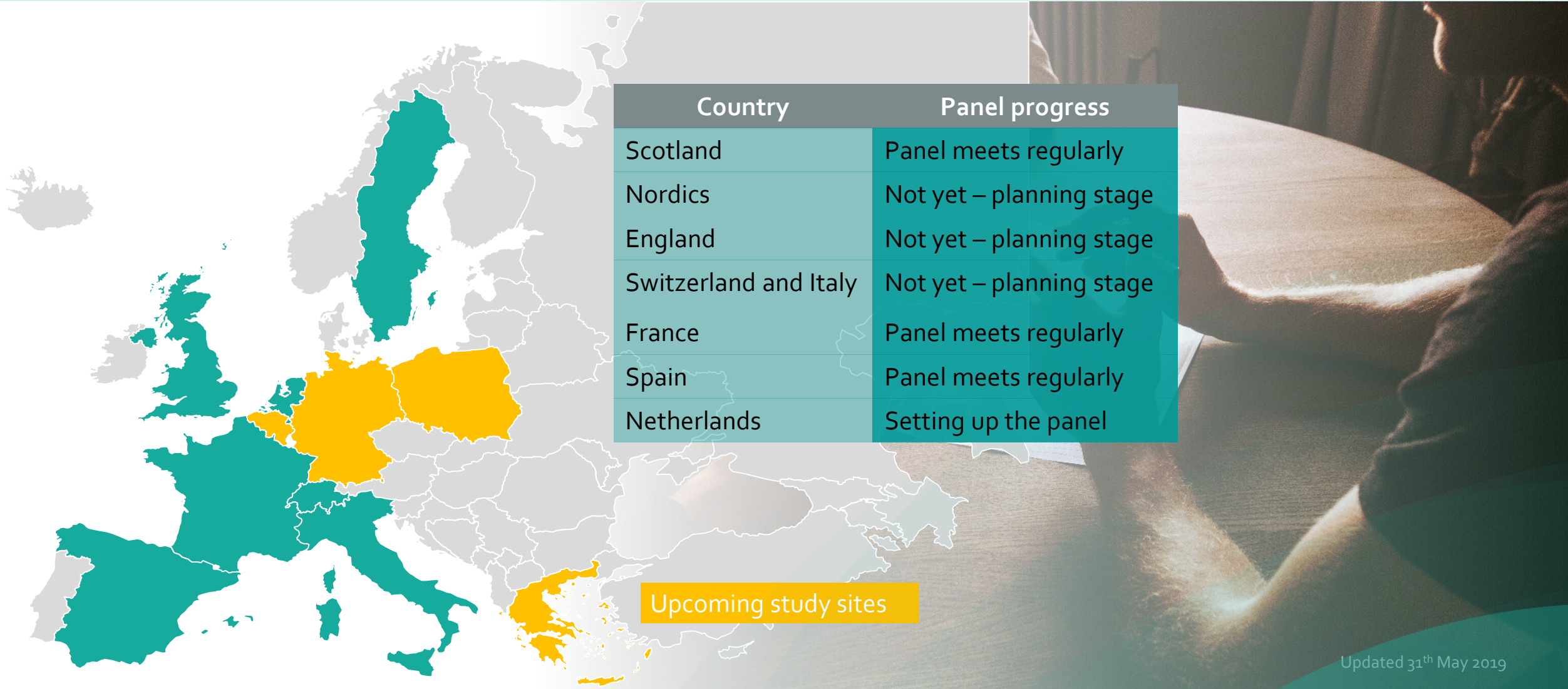
Participants

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



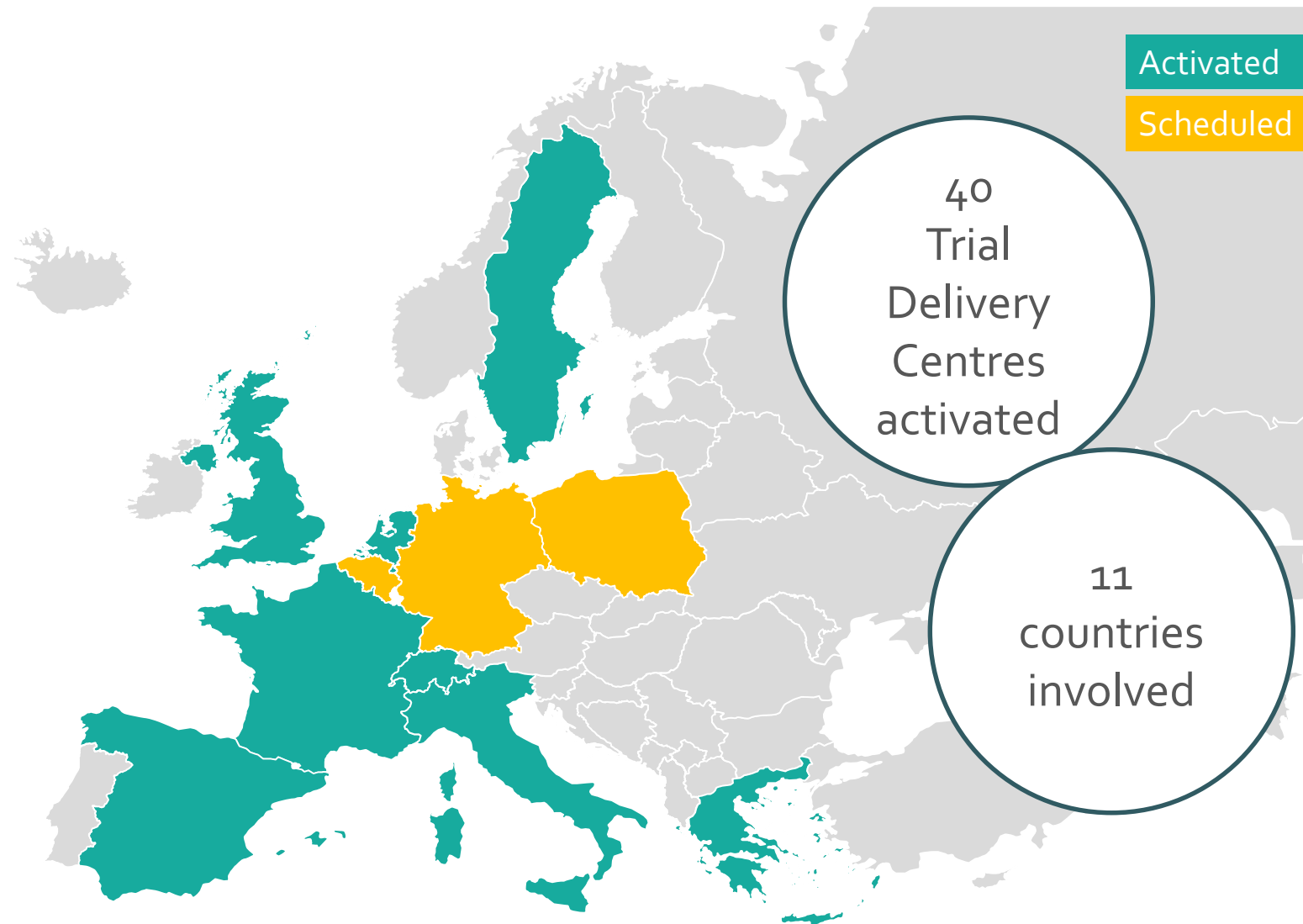
Participant panels so far across the EPAD study



Updated 31th May 2019

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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)
UOXF, Oxford (UK)
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)

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 Trolley Virtual 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

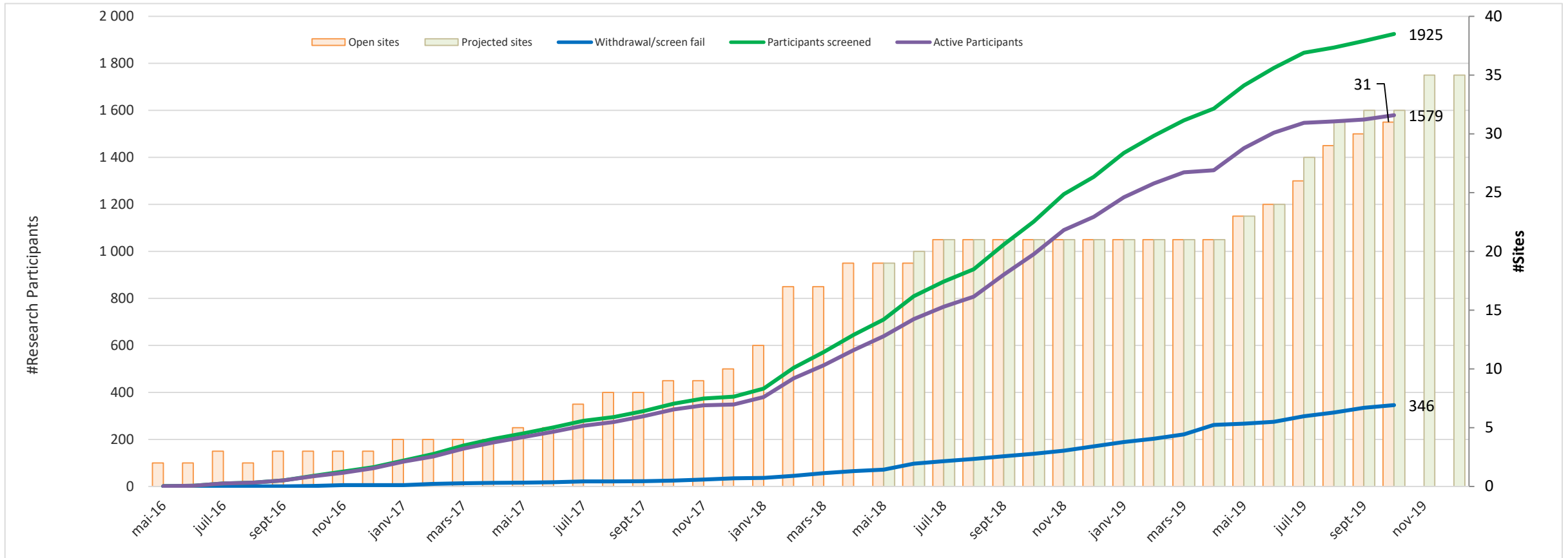
Risk factors

- 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

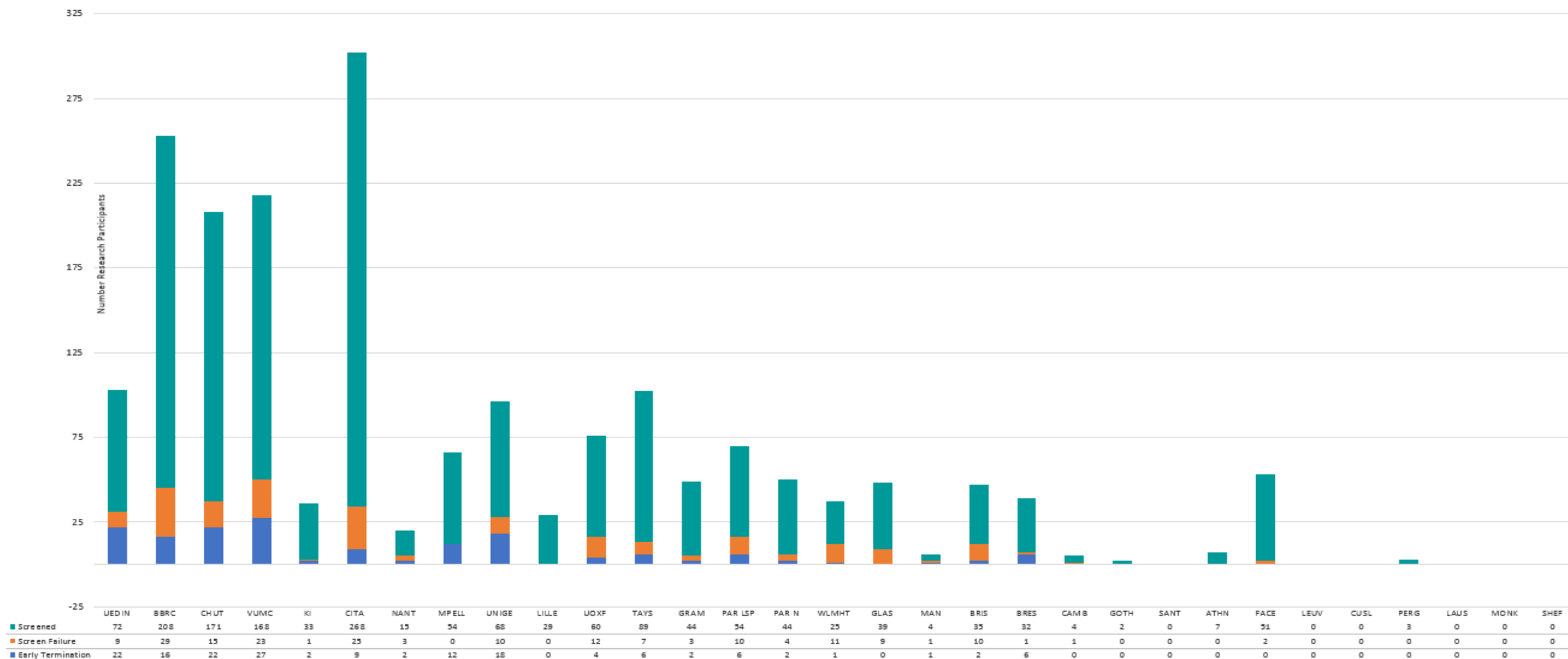
- The Geriatric Depression Scale
- The State-Trait Anxiety Inventory (STAI)
- The Pittsburgh Sleep Quality Index
- The Amsterdam Instrumental Activities of Daily Living Questionnaire
- MMSE (Mini Mental State Examination)
- CDR (Clinical Dementia Rating)

Recruitment Status 24 Oct 2019



Recruitment Status Per Site

24 Oct 2019



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Master PoC protocol

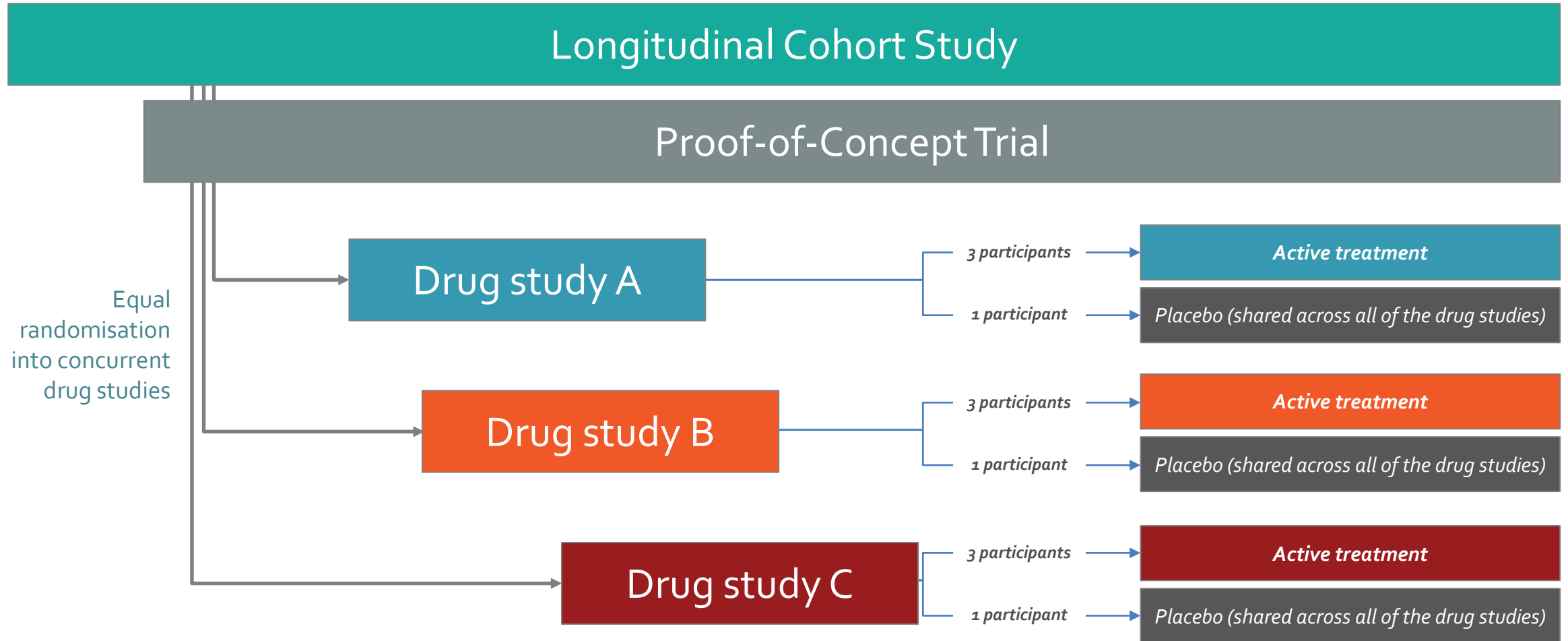
- Description of common framework of the PoC trial and minimum inclusion and exclusion criteria for all interventions

+

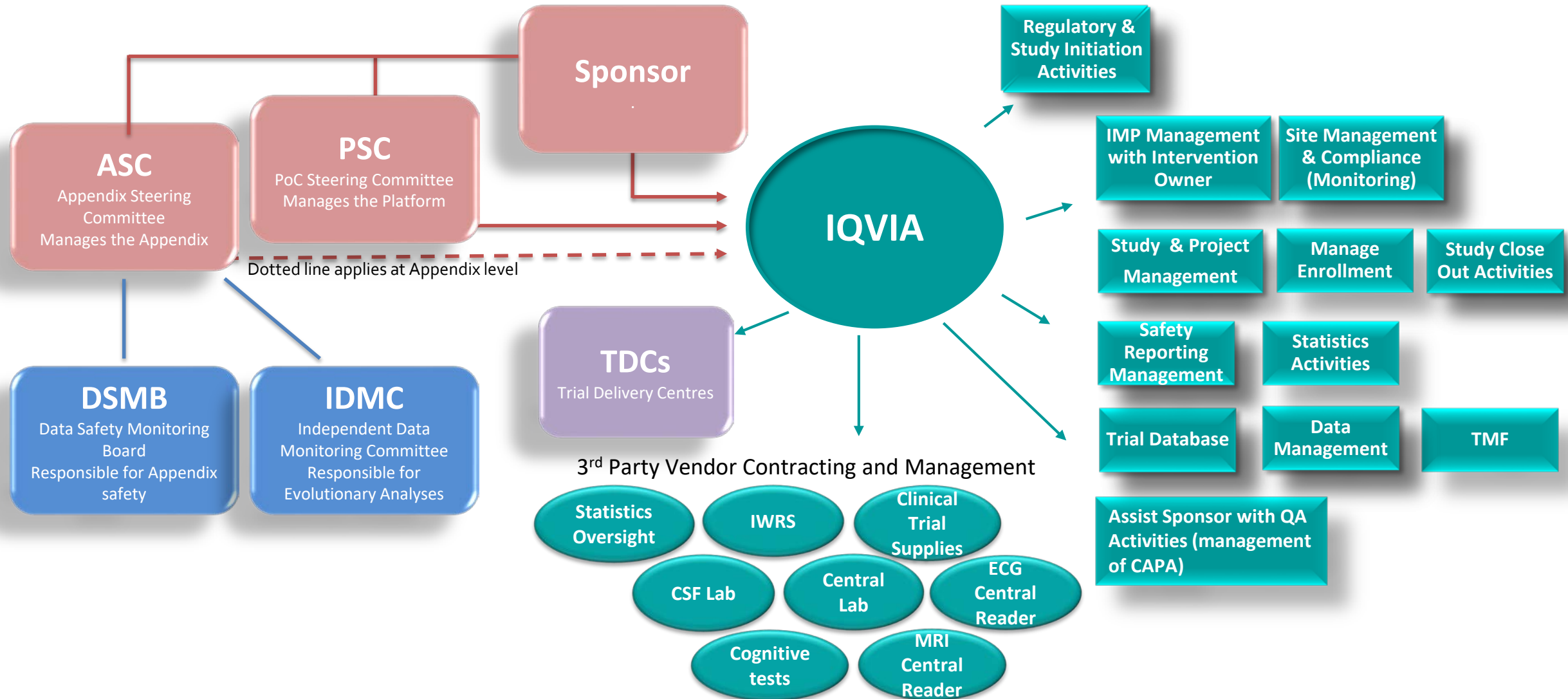


Appendix to the master protocol

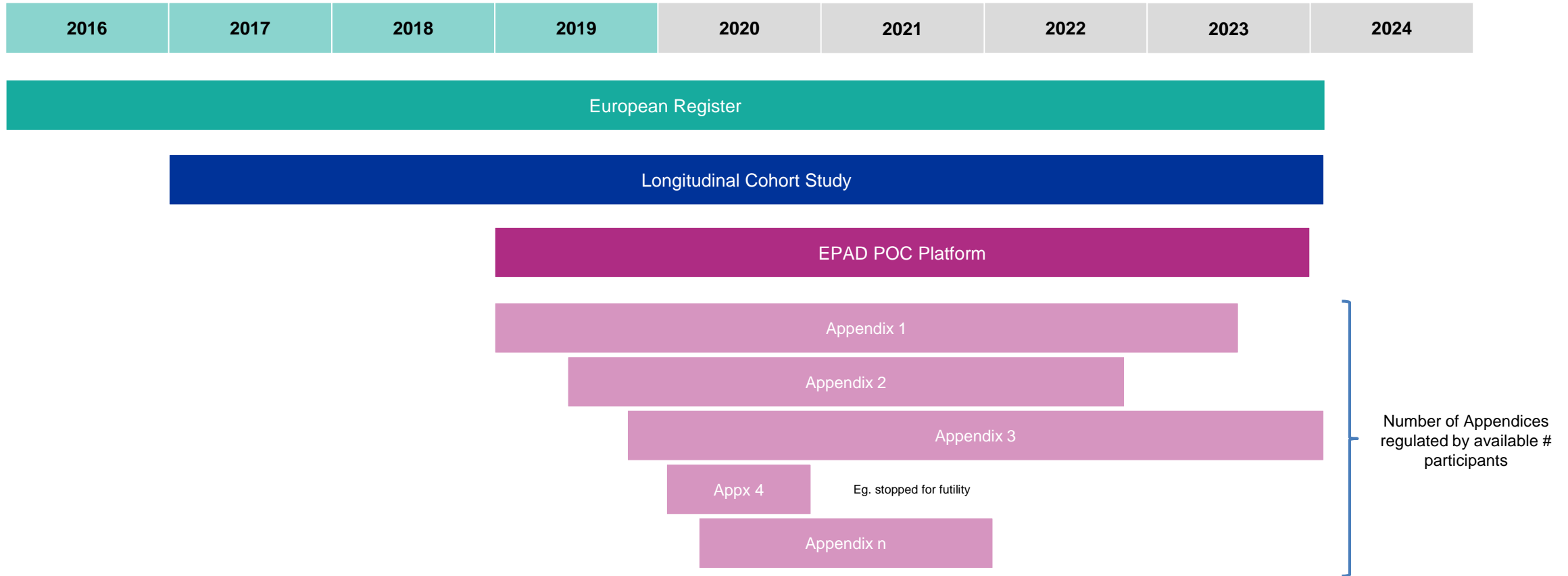
- Specifically for each intervention cohort. Will define the specific information and additional trial elements and inclusion/exclusion criteria



PoC Platform Set-up (Behind the Curtain)



EPAD timelines



The EU Registry /LCS are funded through a grant from Innovative Medicines Initiative (IMI) up till June 2020.

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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
30000
research
participants
over 50 years old



EPAD Longitudinal Cohort Study

UP AND RUNNING IN

25 TDCs
and more than **1900**
research participants enrolled

TRIAL DELIVERY CENTRES

**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

EPAD TDC Network

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

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

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

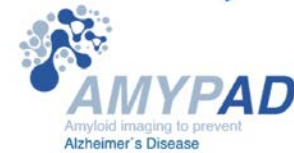
EPAD
Cohort

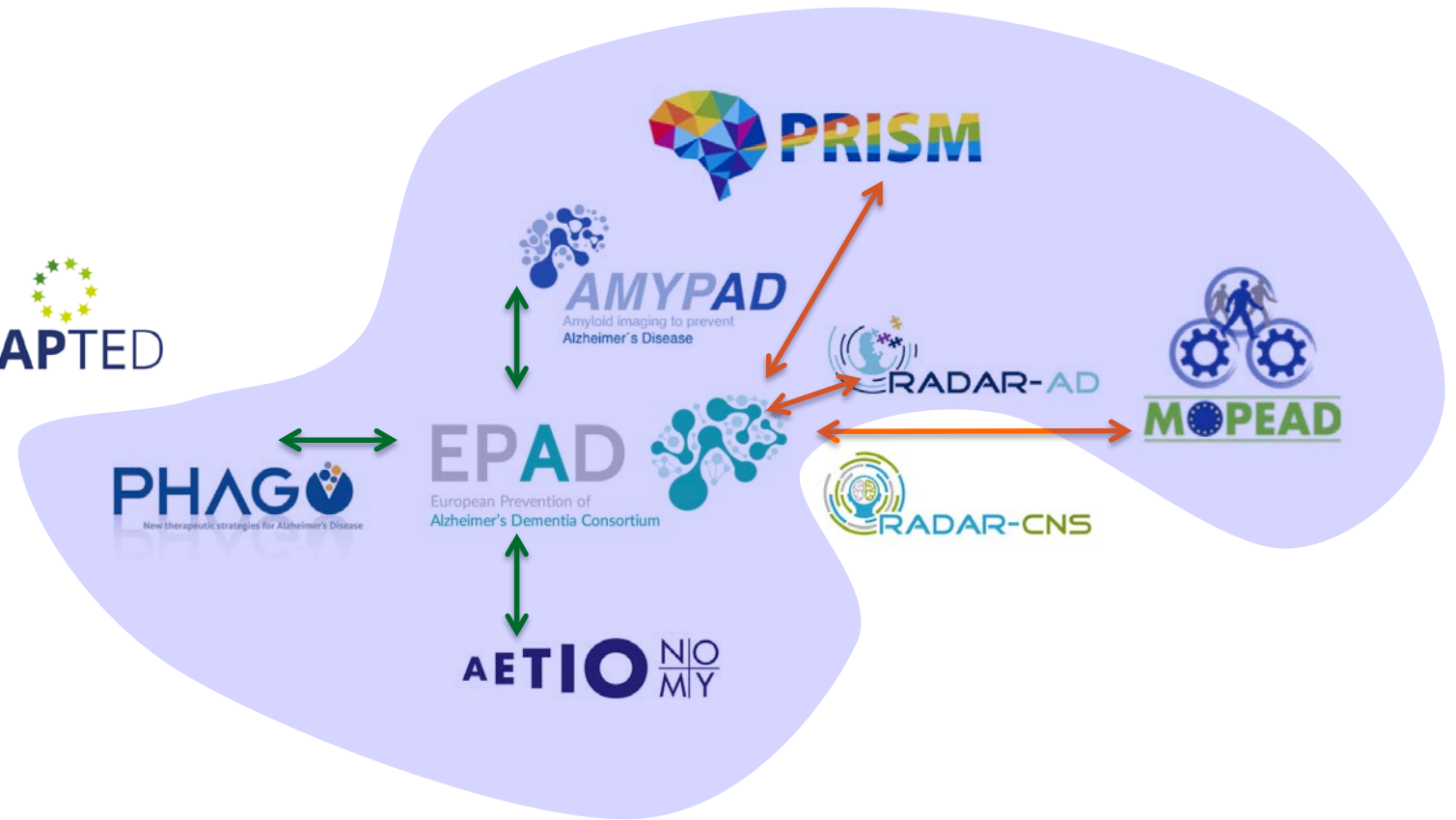
EPAD Trial
Platform

EPAD
L'Academie

- BioBank
- Bolt on Studies

- Data Access
- Participants' Panel





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EPAD LCS Data Management Delivery Team



IQVIA

- **Joseph Milne**
- **Siva Kumar**
- MartinDvořák
- 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?

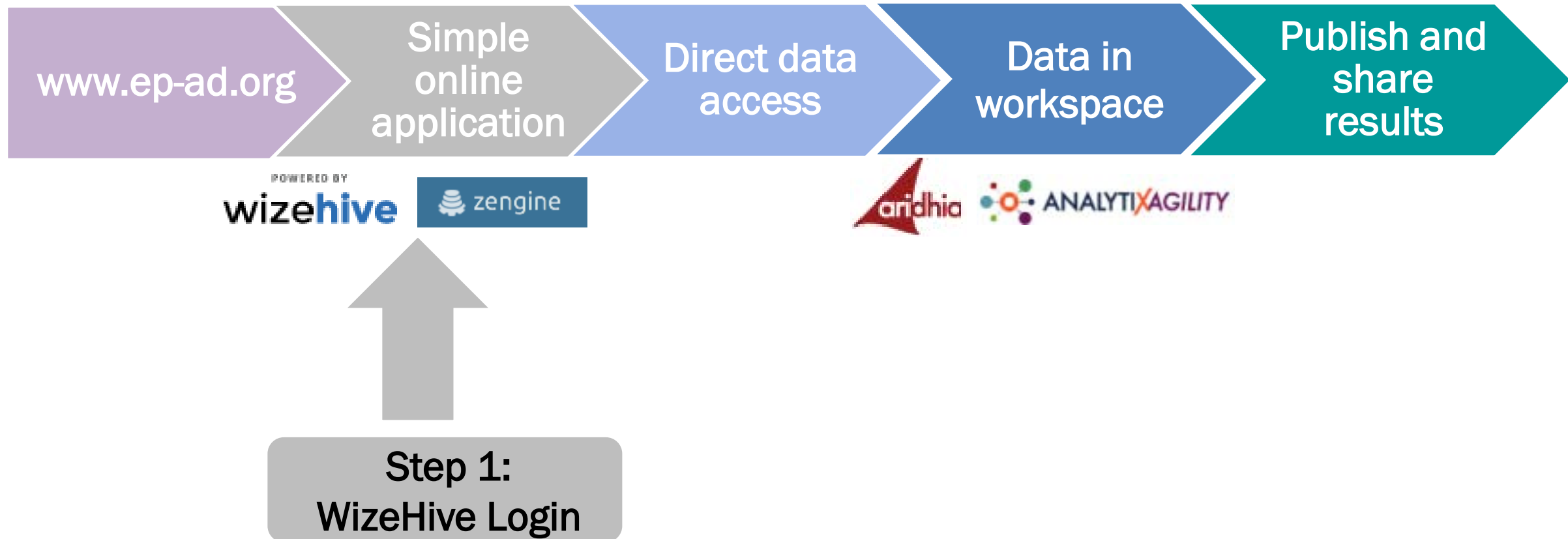


EPAD Research Access Process

<http://ep-ad.org/erap/>

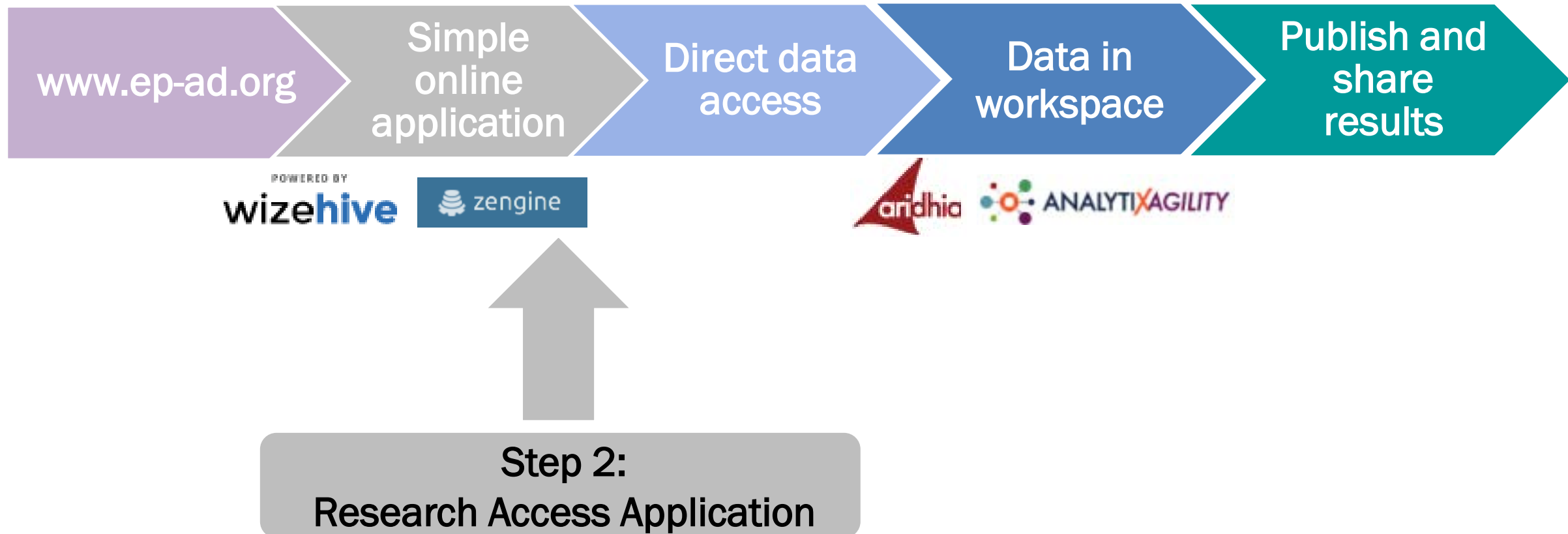
How do you access EPAC LCS Data?

<http://ep-ad.org>



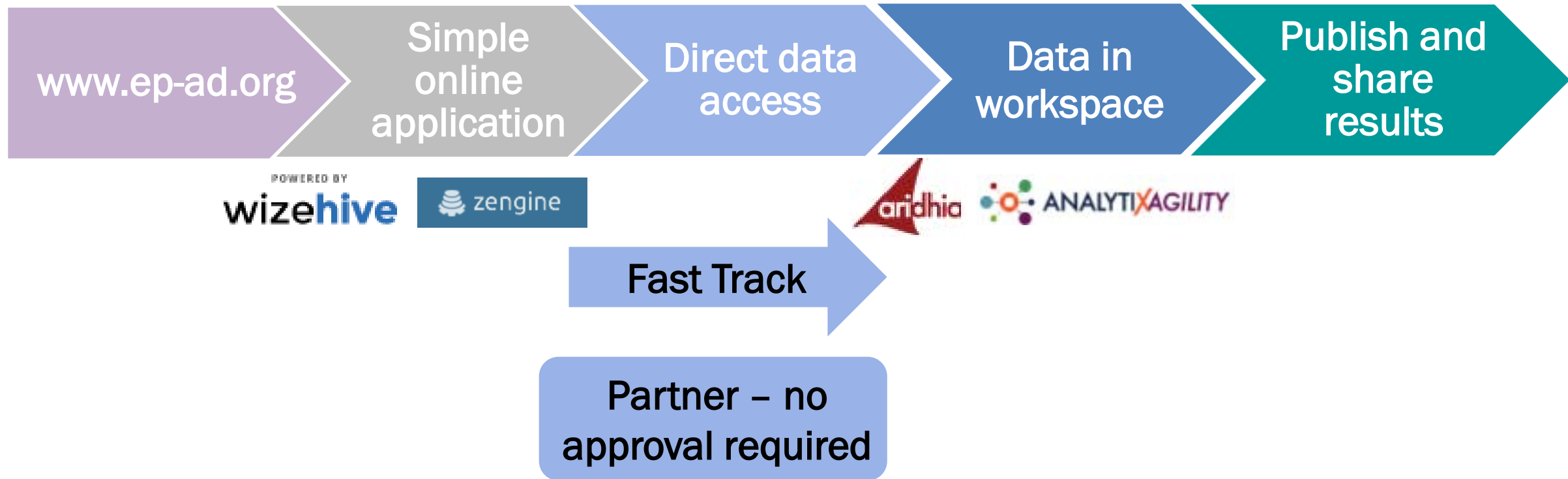
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POWERED BY
wizehive

 **zengine**



 **ANALYTIXAGILITY**

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 |
| ▪ V1500.1 | Embargoed Release: 28/11/20 | Open Data Access: 28/5/21 |

Scientific publications

(All publications available here: <http://ep-ad.org/about/publications/>)

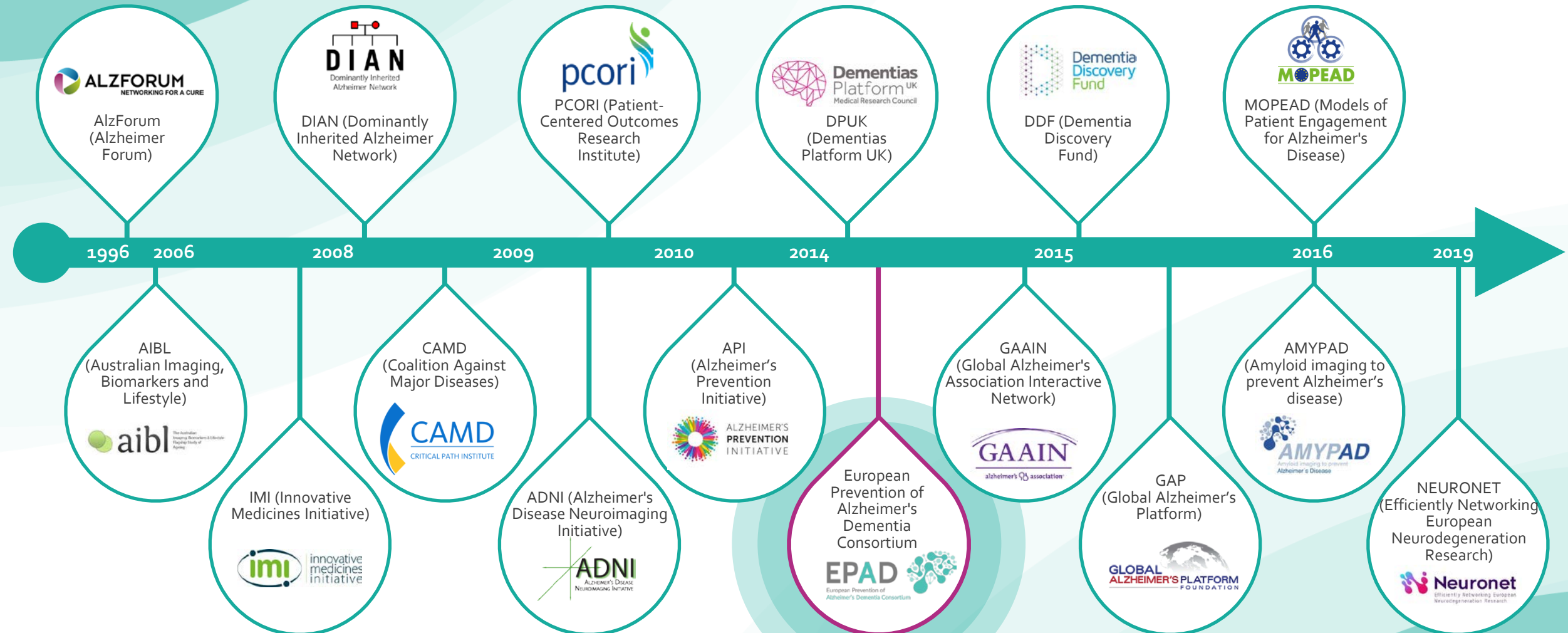
Authors	Date	Title	Journal
CW Ritchie et al.	09/12/2015	Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project	The Lancet Psychiatry
JL Molinuevo et al.	14/03/2016	Ethical challenges in preclinical Alzheimer's disease observational studies and trials: results of the Barcelona summit	Alzheimer's and Dementia
M Mortamais et al.	01/10/2016	Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility	Alzheimer's and Dementia
K Ritchie et al.	01/10/2016	Recommended cognitive outcomes in pre-clinical Alzheimer's disease: consensus statement from the European Prevention of Alzheimer's Dementia (EPAD) Project	Alzheimer's and Dementia
S. Bemelmans et al.	10/11/2016	Psychological, behavioural and social effects of disclosing Alzheimer's Disease biomarkers to research participants – a systematic review	Alzheimer's Research & Therapy
R. Milne et al.	22/02/2017	Ethical issues in the development of readiness cohorts in Alzheimer's disease research	The Journal of Prevention of Alzheimer's Disease
PJ Visser et al.	13/06/2017	Brain Amyloid Pathology and Cognitive Function. Alzheimer Disease Without Dementia?	JAVA
S Saunders et al.	13/12/2017	Evolution and future directions for the concept of mild cognitive impairment	International Psychogeriatrics
R Milne et al.	20/02/2018	Perspectives on Communicating Biomarker-Based Assessments of Alzheimer's Disease to Cognitively Healthy Individuals	Journal of Alzheimer's Disease
JL Molinuevo et al.	13/03/2018	The Rationale Behind the New Alzheimer's Disease Conceptualization: Lessons Learned During the Last Decades	Journal of Alzheimer's Disease

Scientific publications

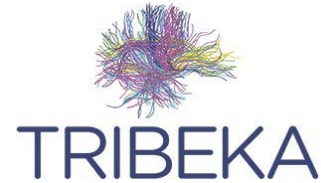
(All publications available here: <http://ep-ad.org/about/publications/>)

Authors	Date	Title	Journal
L Vermunt et al.	28/03/2018	European Prevention of Alzheimer's Dementia Registry: Recruitment and prescreening approach for a longitudinal cohort and prevention trials	Alzheimer's & Dementia
R Milne et al.	16/04/2018	At, with and beyond risk: expectations of living with the possibility of future dementia	Sociology of Health & Illness
E Bunnik et al.	28/08/2018	On the personal utility of Alzheimer's disease-related biomarker testing in the research context	Journal of Medical Ethics
M ten Kate et al.	30/10/2018	Secondary prevention of Alzheimer's dementia: neuroimaging contributions	Alzheimer's Research & Therapy
S Gregory et al.	01/11/2018	Research participants as collaborators: Background, experience and policies from the PREVENT Dementia and EPAD programmes	Dementia
A Solomon et al.	27/12/2018	European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol	BMJ Open
M Smedinga et al.	12/12/2018	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	Journal of Alzheimer's Disease
Ramusino et al.	15/07/2019	Medial temporal lobe atrophy and posterior atrophy scales normative values	NeuroImage: Clinical
Archetti et al	23/07/2019	Multi-study validation of data-driven disease progression models to characterize evolution of biomarkers in Alzheimer's disease	NeuroImage: Clinical
Stirland et al	16/08/2019	Associations Between Multimorbidity and Cerebrospinal Fluid Amyloid: A Cross-Sectional Analysis of the European Prevention of Alzheimer's Dementia (EPAD) V500.0 Cohort	Journal of Alzheimer's Disease

Global fight against AD today: continuum of collaboration



Neuronet is in the cool club.....



Australian Government
National Health and Medical Research Council





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[EPAD Twitter twitter.com/imi_epad](https://twitter.com/imi_epad)



[EPAD Youtube Channel](https://youtube.com/EPADChannel)

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.

