EPAD
European Prevention of
Alzheimer's Dementia Consortium

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

Satlin A, **Ritchie CW**, Kivipelto M, Soloman A, Tom B, Molinuevo JL, Berry S, Barkhof F and Farrar G.

www.ep-ad.org

@IMI_EPAD

@IMIEPAD

IMI EPAD

Disclosures

- I have recently sat on paid advisory boards for Merck, Pfizer, Eisai, Actinogen, Kyowa, Roche and Eli Lilly

The EPAD Consortium

EPAD
European Prevention of Alzheimer's Dementia Consortium

Academia

THE UNIVERSITY of EDINBURGH
UNIVERSITY OF OXFORD
barcelonaβeta Brain Research Center
Karolinska Institutet
VUmc VU University Medical Center Amsterdam
UNIVERSITY OF CAMBRIDGE
MRC Biostatistics Unit
UNIVERSITÉ DE GENÈVE
Radboudumc
CARDIFF UNIVERSITY PRIFYSGOL CAERDYDD
Hôpitaux de Toulouse
Erasmus MC
Inserm
University of Leicester
Fraunhofer FHR
UNIKLINIK KÖLN

SMEs

SYNAPSE
Berry Consultants Statistical Innovation
aridhia
IXICO

Patient Organisation

Alzheimer Europe

Other industry

QUINTILES
Araclon Biotech GRIFOLS

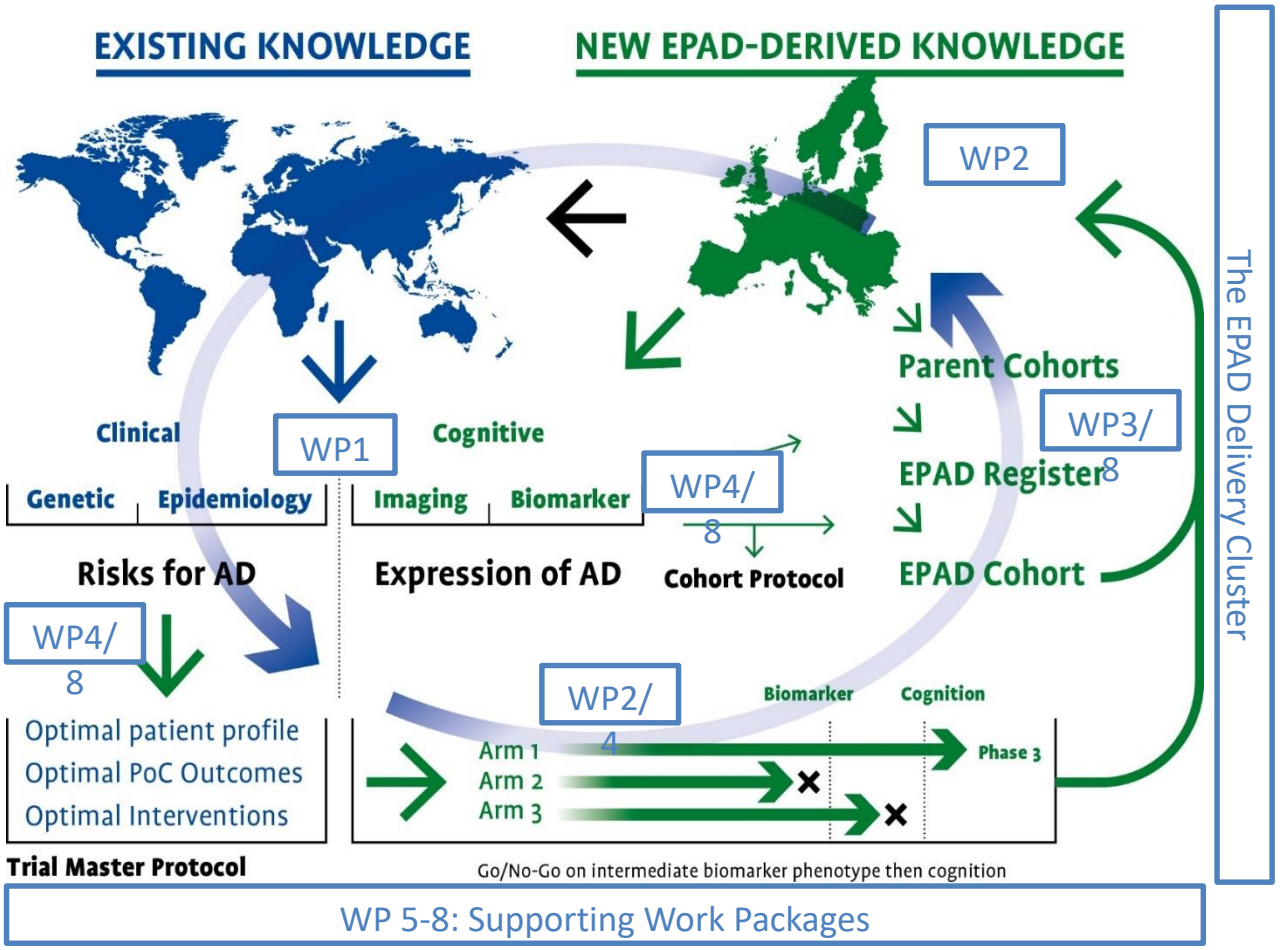
EFPIA

janssen
Eisai
SANOFI
NOVARTIS
Boehringer Ingelheim
Lilly
Lundbeck
Takeda
Roche
AC IMMUNE
Biogen
AMGEN
Pfizer
Inspired by patients. Driven by science.

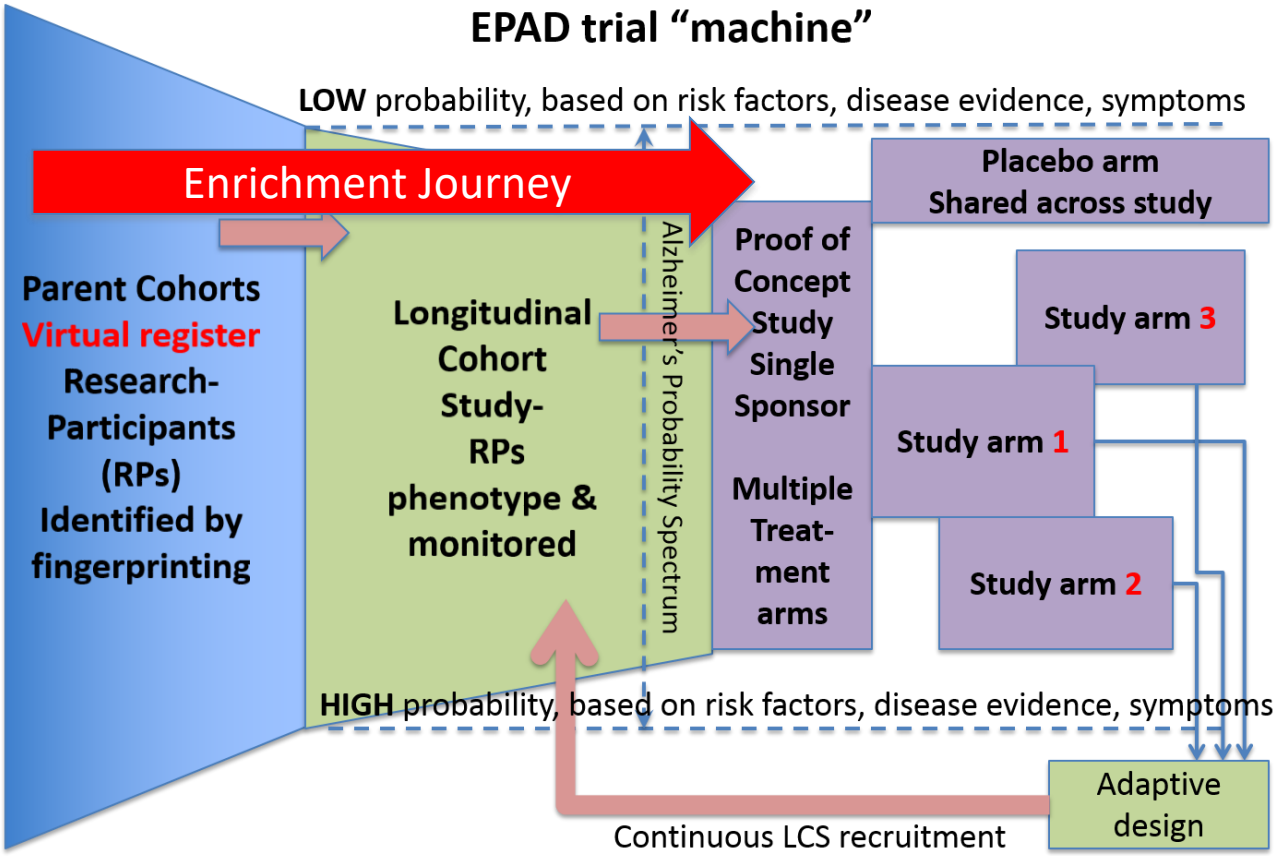
AMYPAD
UCL
GE
Piramal

www.ep-ad.org

The EPAD Project Structure



The EPAD Flow



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)

Making sure we have the right participants in the EPAD Longitudinal Cohort Study (LCS)

- 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

EPAD Neuropsychological Examination (ENE)

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)

ELSEVIER

Alzheimer's & Dementia ■ (2016) 1-25

Alzheimer's & Dementia

Review Article

Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility

M. Mortamais[a,b,1], J. A. Ash[c,1], J. Harrison[d,e], J. Kaye[f], J. Kramer[g], C. Randolph[h], C. Pose[a], B. Albala[i], M. Ropacki[j], C. W. Ritchie[k], K. Ritchie[a,b,*]

ELSEVIER

Alzheimer's & Dementia ■ (2016) 1-10

Alzheimer's & Dementia

Perspective

Recommended cognitive outcomes in preclinical Alzheimer's disease: Consensus statement from the European Prevention of Alzheimer's Dementia project

Karen Ritchie[a,b,*,1], Michael Ropacki[c,1], B. Albala[d], John Harrison[e,f], Jeffrey Kaye[g], Joel Kramer[h], Christopher Randolph[i], C. W. Ritchie[j]

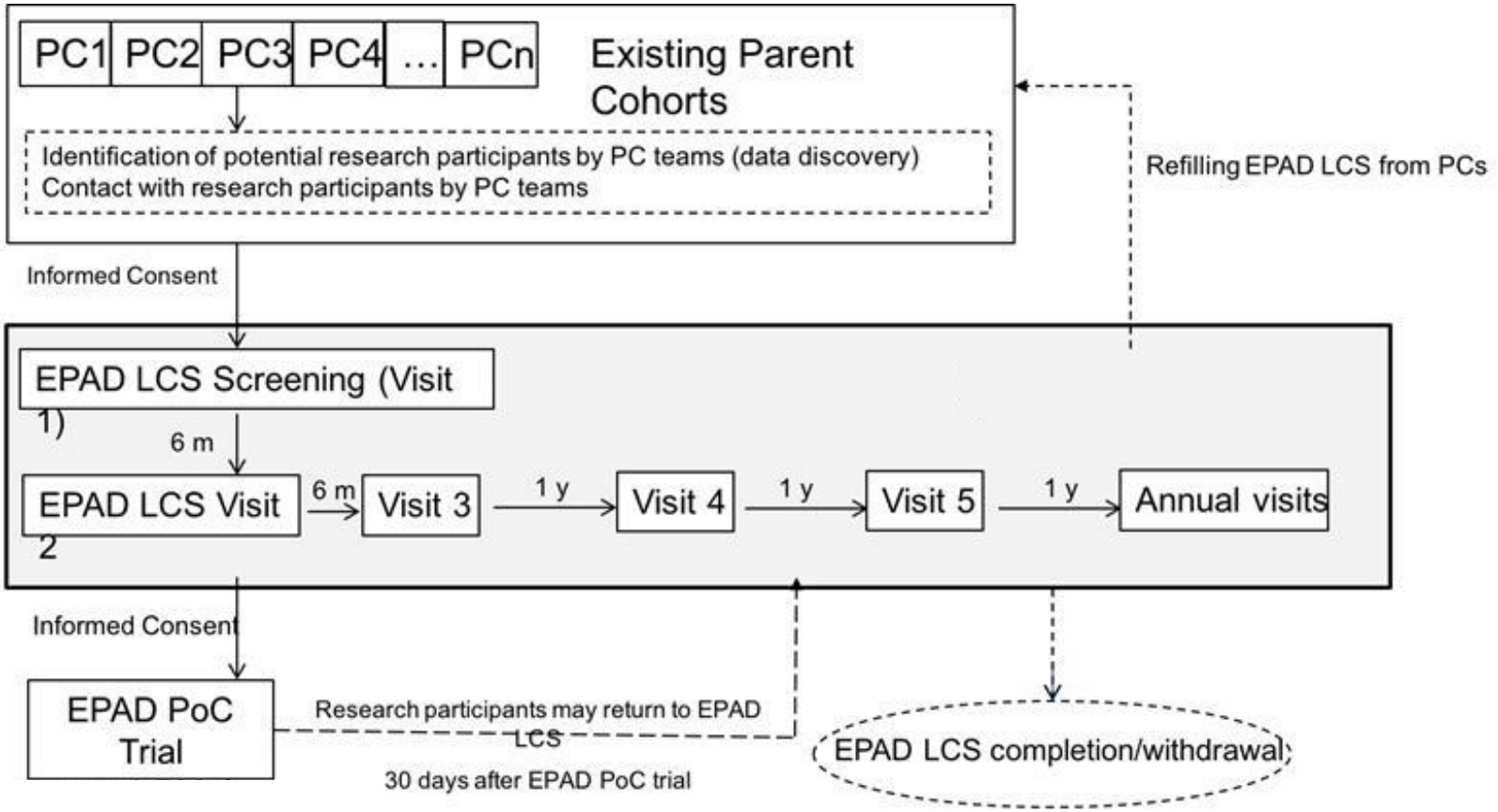
Biomarker Outcomes

- 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

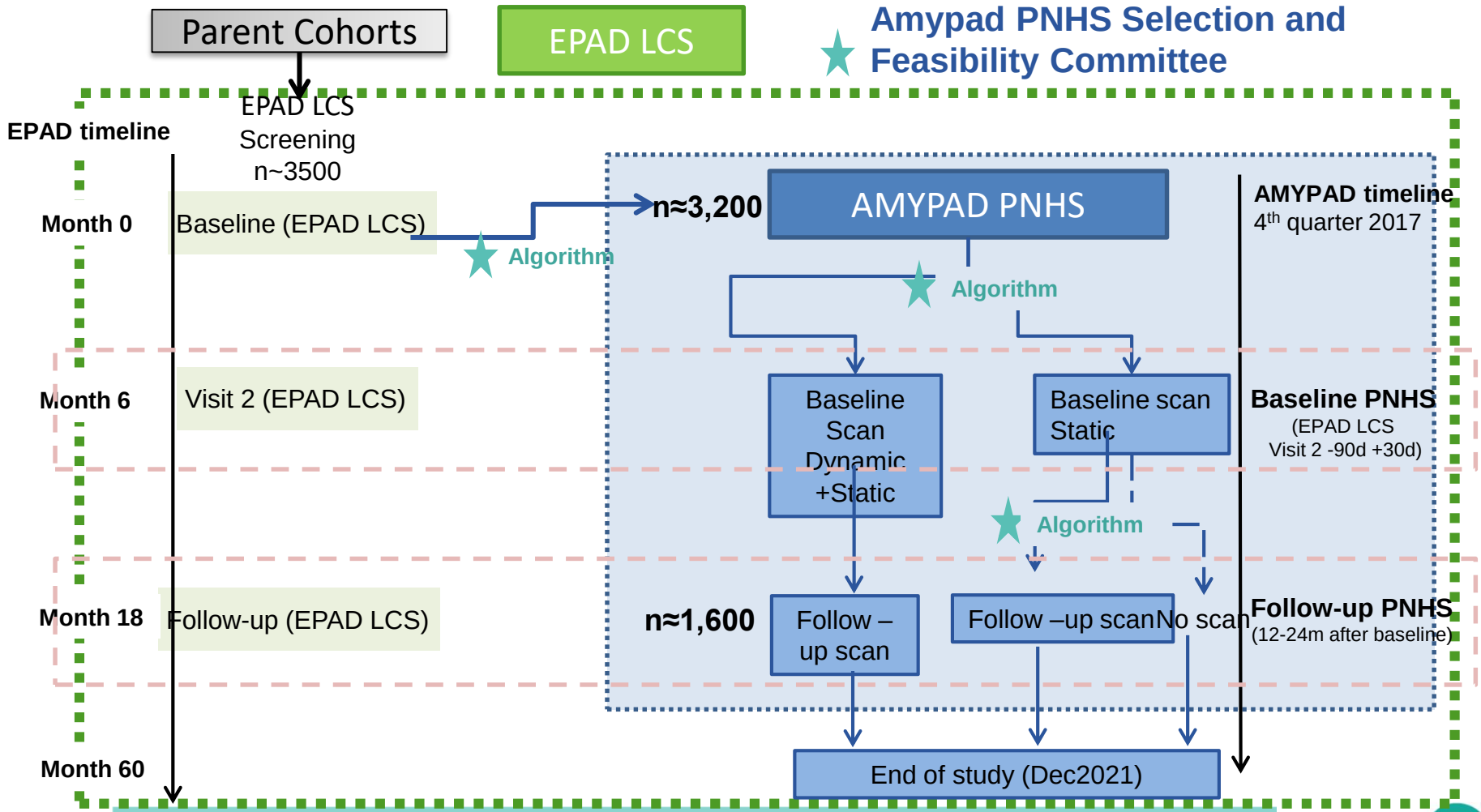
- Other clinical outcomes
  - Depression: 30-item Geriatric Depression Scale (GDS)
  - Anxiety: State-Trait Anxiety Inventory (STAI)
  - Sleep: Pittsburgh Sleep Quality Index
  - Everyday functioning: Amsterdam Instrumental Activities of Daily Living Questionnaire
- Socio-demographic and lifestyle factors,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

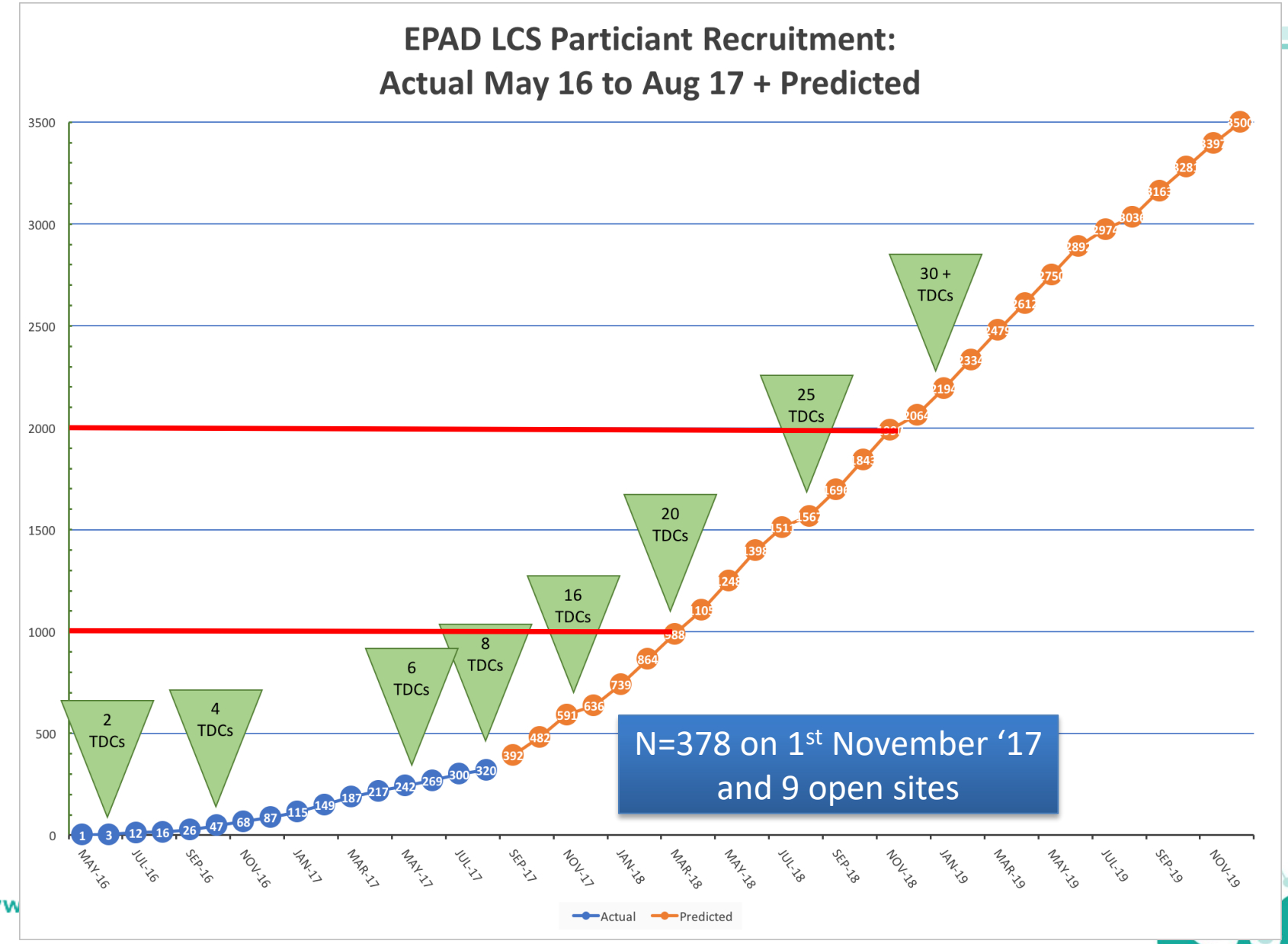


[1] *Once recruitment is completed, at any given time there should be approx. 6,000 research participants in the EPAD LCS and approx. 1,500 in the EPAD PoC, hence the need to replenish each as participants are lost through attrition.*

AMYPAD Prognostic and Natural History Study overview



EPAD LCS Participant Recruitment



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?

Current Database

	Whole Population (n=374)	Full analytical dataset (n=232)	P-value
Age (mean[SD])	66.4 [6.3]	66.2[6.1]	NS
Gender (%M)	49%	48%	NS
Years of Education (mean [SD])	14.3 [3.8]	14.2[3.6]	NS
Family History +	74%	74.4 %	NS
CDR (% CDR=0.5)	13%	15.4%	NS
MTA Score >= 1	14%	13.5 %	NS
ApoEe4 + (n=248)	NA	e4/e4 5% e4/ - 41%	NA
CSF Ab42 (mean[SD])	NA	1296 pg/ml (401 pg/ml)	NA
CSF Tau (mean [SD])	NA	225.3 pg/ml (99.7 pg/ml)	NA
CSF pTau (mean [SD])	NA	20 pg/ml (10.7 pg/ml)	NA
% Amyloid Positive (CSF Ab >1,000 pg/ml)	NA	28%	NA

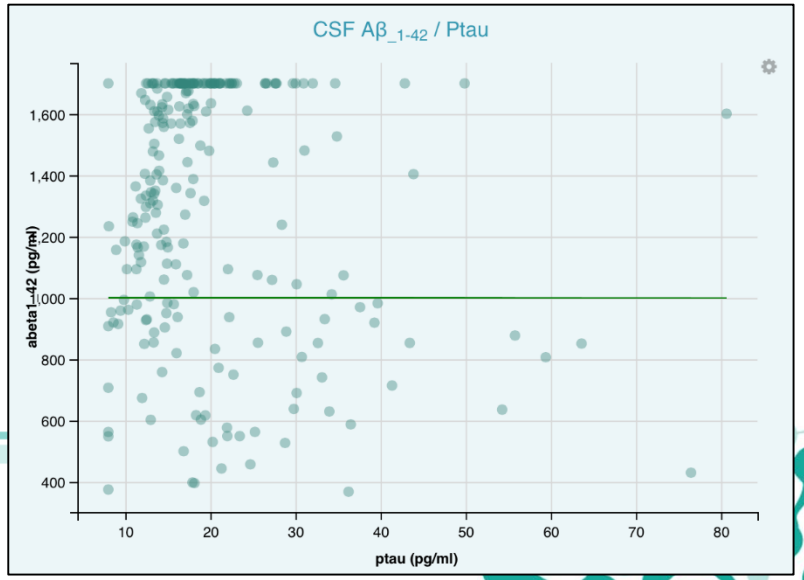
What proportion of current LCS research participants are amyloid positive on CSF?

Amyloid status summary

	CDR 0	CDR 0.5	Total
Amyloid positive (CSF $A\beta_{1\text{-}42} < 1000$ pg/ml)	47	18	**65**
Amyloid grey zone (CSF $1000 \leq A\beta_{1\text{-}42} \leq 1200$ pg/ml)	23	2	**25**
Amyloid negative (CSF $A\beta_{1\text{-}42} > 1200$ pg/ml)	130	12	**142**
Total	**200**	**32**	**232**

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.



EPAD
European Prevention of Alzheimer's Dementia Consortium

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

	Odds Ratio	95% Confidence Interval	P-value
Gender (Male)	1.39	0.68 – 2.90	0.36
Age at baseline	1.08	1.01 – 1.15	0.01
ApoEe4 carrier	2.6	1.27 – 5.48	0.001
Average MTA Score	1.56	0.66 – 3.63	0.29
Family History of AD in FDR	3.1	1.29 – 8.01	0.01
CDR Score	13.49	0.41 – 29.14	0.24
RBANS Total	0.97	0.94 – 0.99	0.09

EPAD
European Prevention of Alzheimer's Dementia Consortium

From parent cohorts what is the predictive value of key variables that could be used for selection?

	ApoEe4 -	ApoEe4 +
Amyloid Negative	96	61
Amyloid Positive	23	38
	NPV = 96/119 (80.6%)	PPV = 38/99 (38%)
	Family History -	**Family History +**
Amyloid Negative	44	123
Amyloid Positive	12	54
	NPV =44/56 (78.6%)	PPV = 54/177 (30.5%)
	CDR 0	**CDR 0.5**
Amyloid Negative	149	17
Amyloid Positive	48	17
	NPV =149/197 (75.6%)	PPV = 17/34 (50%)

From parent cohorts what is the predictive value of key variables that could be used for selection?

- **If CDR = 0.5 AND ApoEe4+ = 11/15 amyloid positive (73.3%)**
- If CDR = 0.5 AND ApoEe4- = 6/18 amyloid positive (33.3%)

- If CDR = 0 AND ApoEe4+ = 26/83 amyloid positive (31.3%)
- If CDR = 0 AND 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 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

Sample Size	Baseline	Year 1	Year 2	Year 3	Year 4
500	V500.0	V500.1	V500.2	V500.3	V500.4
1000	V1000.0	V1000.1	V1000.2	V1000.3	V1000.4
2000	V2000.0	V2000.1	V2000.2	V2000.3	V2000.4
3000	V3000.0	V3000.1	V3000.2	V3000.3	V3000.4

Increasing Value for Novelty Sample Access*

Increasing Value for Novelty Sample Access*

www.ep-ad.org

*Exception is genetic analysis

EPAD
European Prevention of
Alzheimer's Dementia Consortium

www.ep-ad.org

EPAD
European Prevention of Alzheimer's Dementia Consortium

Acknowledgments

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.

efpia

imi innovative medicines initiative