The European Prevention of Alzheimer's Dementia (EPAD); Summary of First Formal Data Lock (EPAD V500.0) and predictors of amyloid status

Ritchie CW, Muniz-Terrera G, Kivipelto M, Solomon A, Tom B, van der Geyten S and Molinuevo JL

Craig Ritchie
Centre for Dementia Prevention
Universith of Edinburgh

@craig_ritchie68

Declaration of Interests

- I have provided consultancy services and received grant funding from the following commercial organizations:

- Actinogen, Allergan, Biogen, Eisai, Alector, Janssen, MSD, Lundbeck, Prana Biotechnology, Abbvie, Roche, Eli Lilly and Pfizer

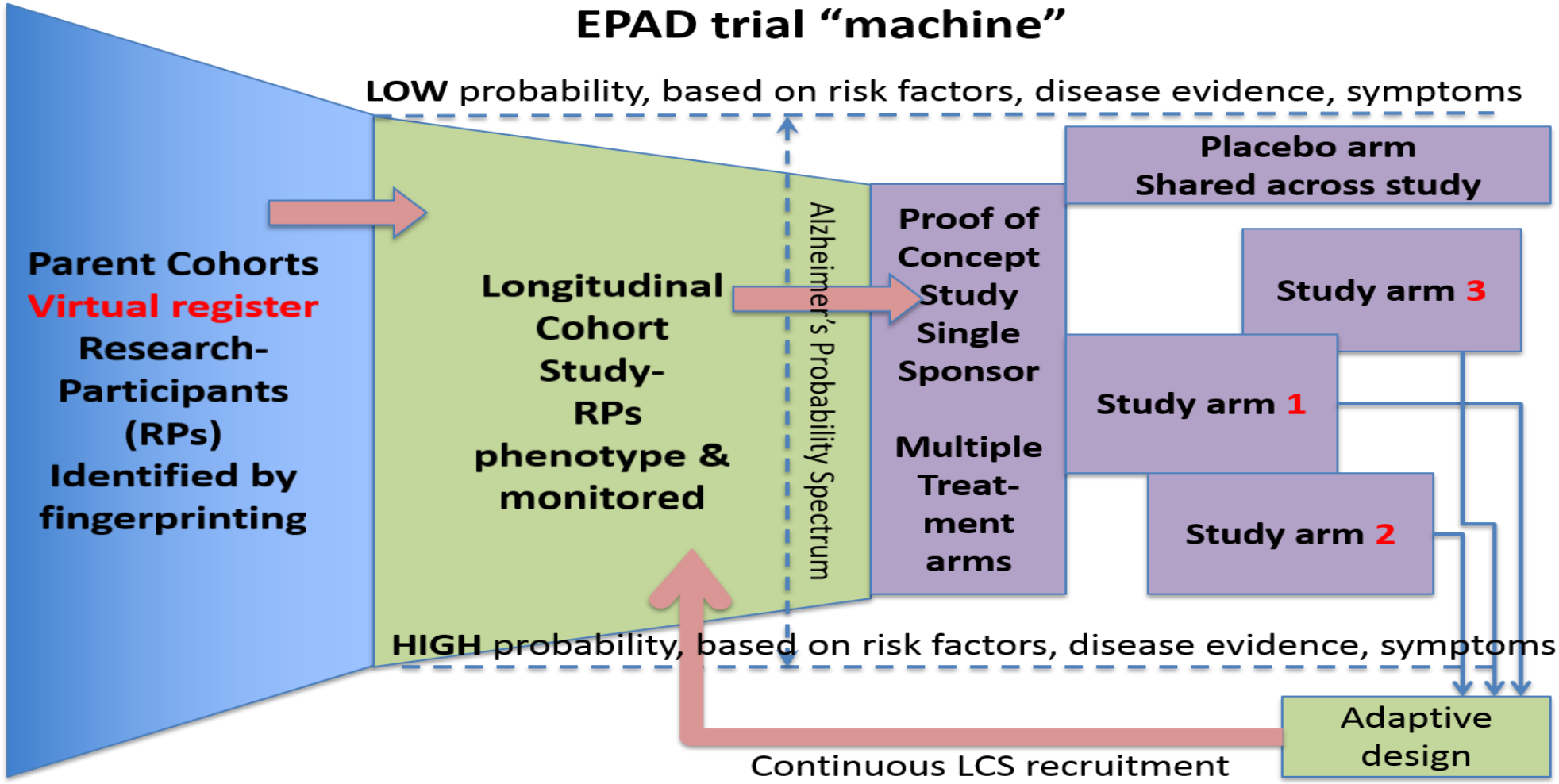
Overview of Presentation

- Brief summary of the EPAD Project and Progress

- The V500.0 Dataset
  - Rationale
  - Results

- EPAD Longitudinal Cohort Study as a Readiness Cohort for the PoC Trial
  - Predictors of Amyloid Positivity to improve readiness

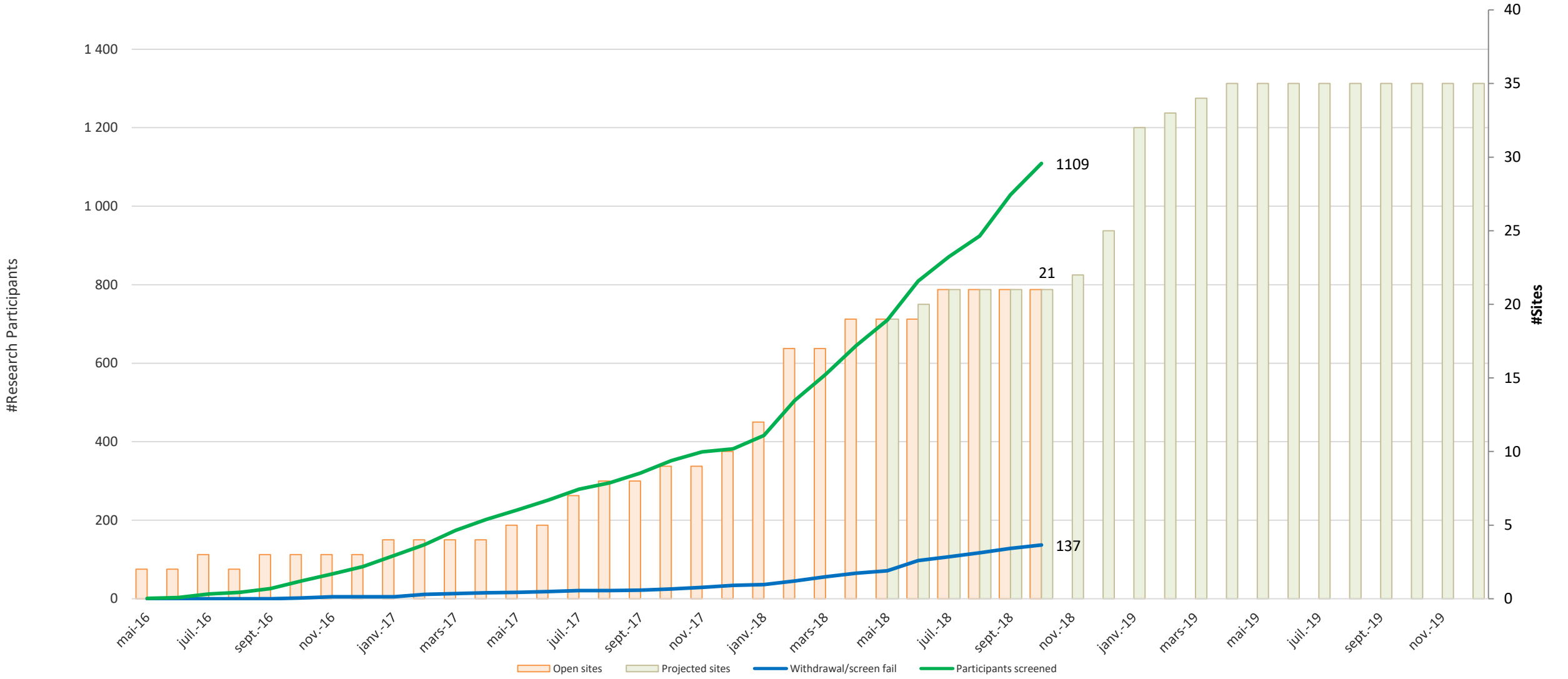
EPAD Programme Overview



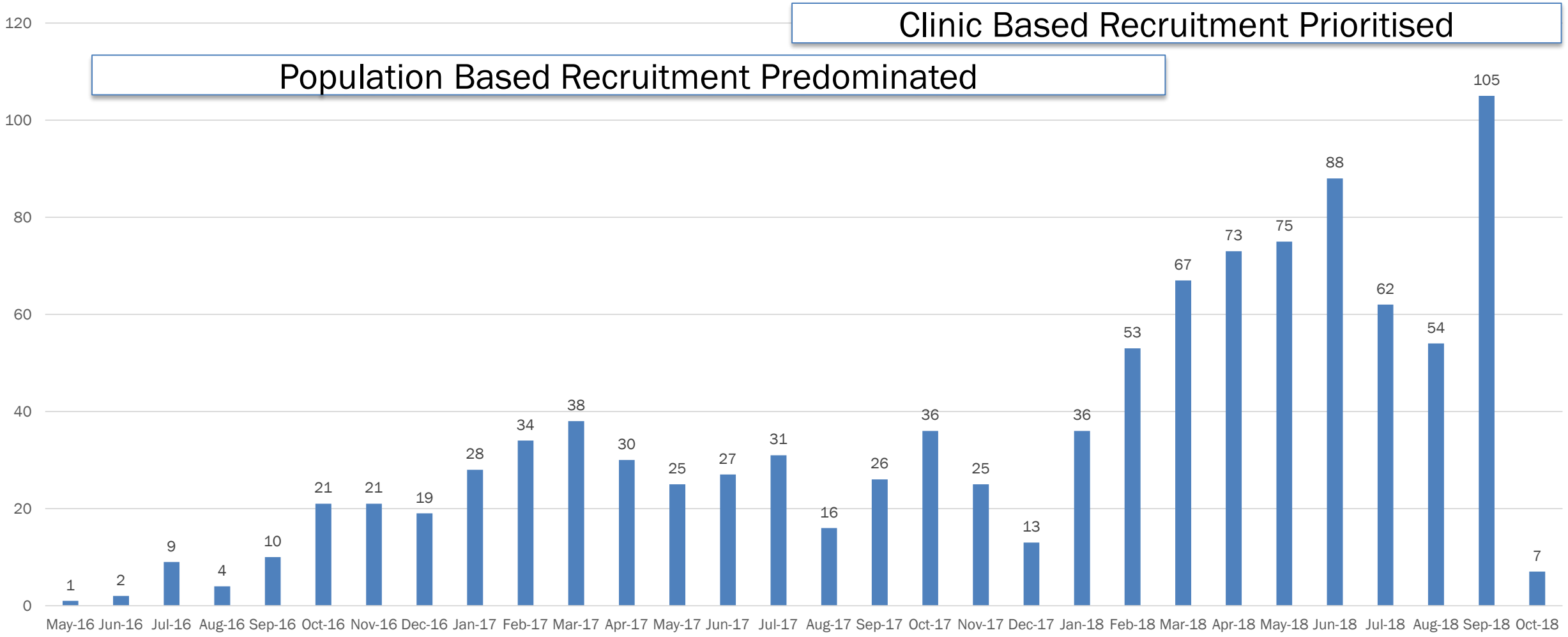
EPAD Longitudinal Cohort Study

- Readiness
- Disease Modeling
- Run In Data

EPAD Longitudinal Cohort Study Recruitment update



Screening Numbers per Study Month



The EPAD V500.0 Dataset

- **Rationale**
  - Perpetual recruitment so had to create interim data locks
  - Transparency on data set being used by researchers
    - Aids comparisons of research outputs and meta-analysis
  - Operationally more coordinated
    - Imaging, biomarker and genetic data embedded in main dataset

- **V** = Version
- **500** = the number of sequentially recruited research participants in dataset
- **.0** the study visit the dataset includes up to

- Summer 2019 – expect on basis of current recruitment V1500.0 and V500.1
- 6-month within consortium privileged access then all data on open data access platform – still to be agreed exact details

The EPAD V500.0 Dataset

- Results[1]

  – All outputs grouped by CDR and Amyloid Status
    - (CSF Aβ <1,000pg/ml defined as Amyloid Positive)

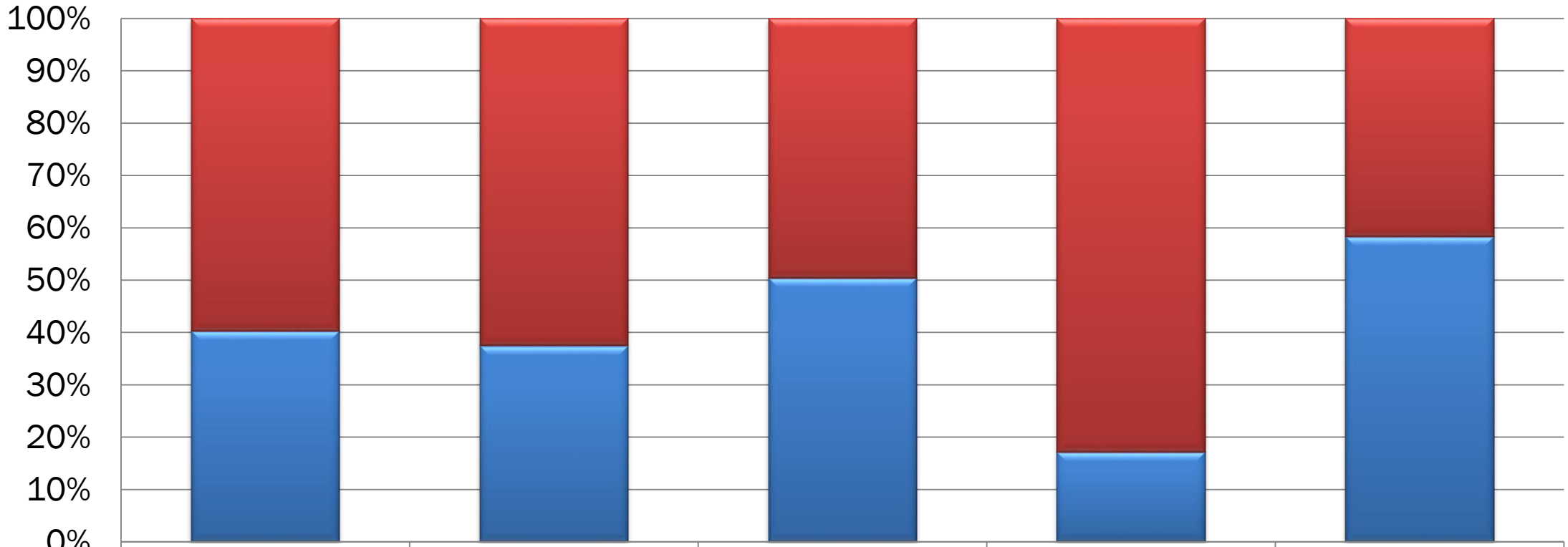
  – Key variables
    - **Demographics and ApoE status**
    - **Cognition**
    - MRI Imaging (Volumes – Fazeka and Scheltens Scores)
    - Other Clinical – Functional, Sleep, Depression and Anxiety

[1]Ritchie CW et al. **The European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study: Baseline Data Release V500.0.** (In Press) *JPAD* 2018

EPAD V500.0 Demographics and ApoE Status

	Total sample (n=500)	CDR 0 Amyloid- (n=251)	CDR 0 Amyloid+ (n=118)	CDR 0.5 Amyloid- (n=37)	CDR0.5 Amyloid+ (n=37)
Age Mean (SD)	66.3(6.6)	64.9(5.9)	65.9 (6.5)	69.5(7.6)	71.8(6.5)
Gender					
F	261(52%)	140(56%)	60(51%)	19(51%)	13(35%)
M	236(47%)	111(44%)	57(49%)	18)49%)	24(65%)
Marital Status					
Divorced	54(11%)	19(7%)	15(13%)	7(19%)	6(16%)
Married	275(75%)	198(79%)	87(74%)	26(70%)	27(73%)
Single	36(7.2)	18(7%)	6(5%)	3(8%)	3(8%)
Widowed	32(64%)	16(6%)	9(7%)	1(3%)	1(3%)
Education (years)	14.(3.7)	14.2(3.6)	13.9(3.8)	13.7(3.7)	14.1(3.9)
APOE Status					
APOE4 +	189(37%)	91 (36%)	59(50%)	6 (16%)	21(56%)
APOE4 -	282 (56%)	152(61%)	58(49%)	29(79%)	15(41%)
Family history					
No	56(11%)	18(7%)	5(4%)	16(41%)	13(35%)
Yes	293(59%)	162(65%)	85(72%)	6(16%)	11(30%)

EPAD V500.0 ApoE Status by Amyloid and CDR Status



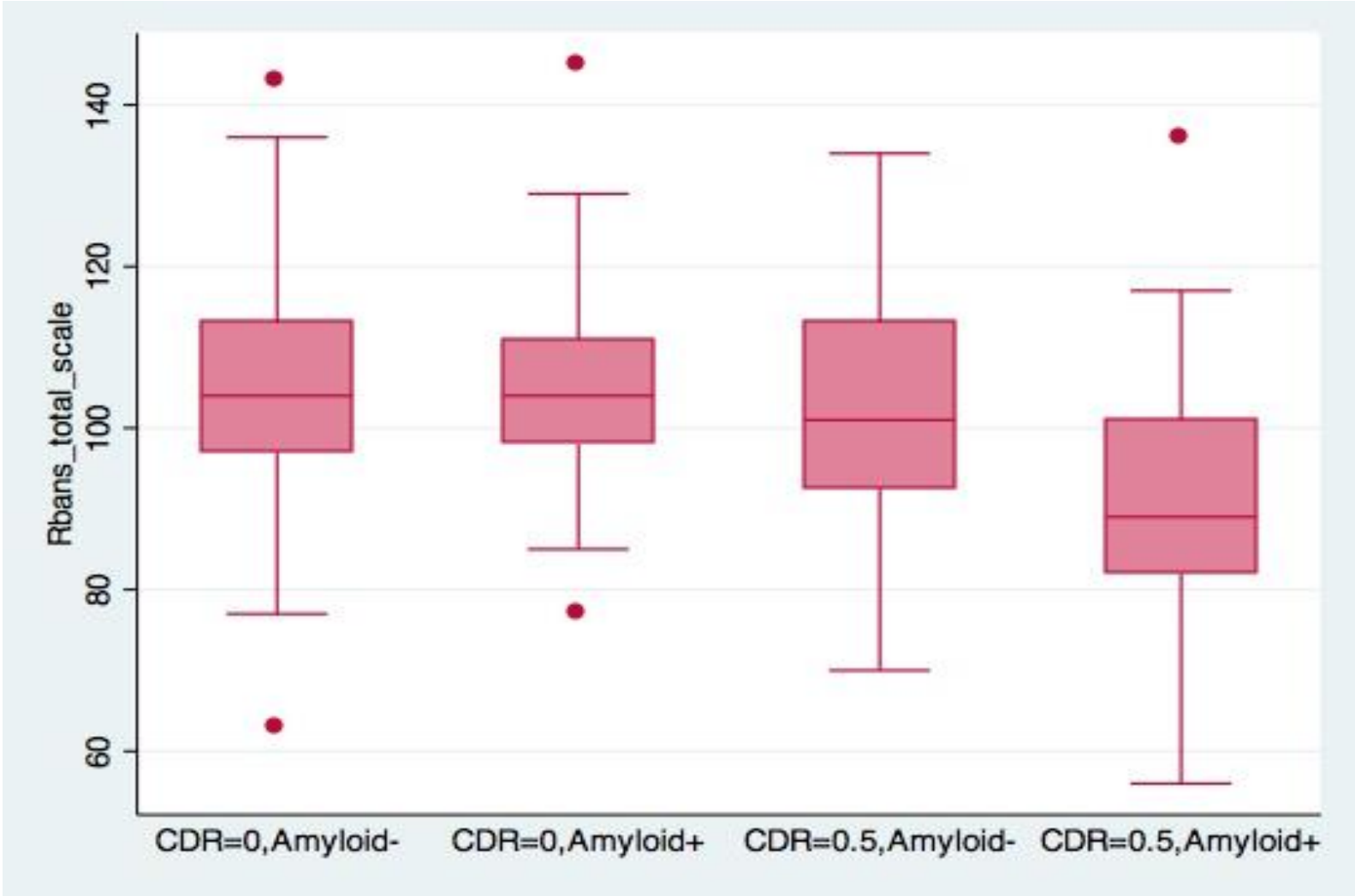
	Total	CDR = 0 and Amyloid Negative	CDR = 0 and Amyloid Positive	CDR = 0.5 and Amyloid Negative	CDR = 0.5 and Amyloid Positive
ApoEe4 -	282	152	58	29	15
ApoEe4 +	190	91	59	6	21

EPAD V500.0 Cognitive Outcomes[1]

	Total Sample (n=500)	CDR 0 Amyloid – (n=251)	CDR 0 Amyloid + (n=118)	CDR 0.5 Amyloid – (n=37)	CDR 0.5 Amyloid + (n=37)
RBANS Total (mean/SD)	103.1(12.7)	105.2(12.0)	104.4(10.5)	102.6(14.7)	91.5(14.7)
RBANS DMI (mean/SD)	102.5(13.5)	103.9(11.0)	104.0(12.3)	103.4(14.7)	89.9(19.5)
RBANS List Learning	28.2(4.7)	28.8 (4.2)	29.3(4.2)	27.4(4.6)	23.05(5.4)
RBANS Story Memory	18.19(1.9)	18.5 (2.7)	18.7(2.9)	17.3(3.7)	15.7(4.4)
RBANS Figure Recall	14.2(3.9)	14.5 (3.4)	15.0(3.3)	13.6(3.9)	10.6(4.8)
RBANS Figure Copy	18.6(1.9)	18.6 (2.0)	18.6(1.7)	18.6(2.1)	18.2(1.8)
RBANS Line Orientation	18.0(2.2)	18.0 (2.2)	18.4(1.8)	17.9(3.2)	17.6(2.1)
RBANS Picture Naming	9.8(0.9)	9.8 (0.7)	9.9(0.4)	9.3(2.3)	9.8(0.6)
RBANS Semantic Fluency	19.2(5.6)	20.2 (5.3)	19.4(5.5)	18.9(4.9)	16.4(5.0)
RBANS Digit Span	9.5(2.3)	9.6(2.3)	9.6(2.3)	9.5(1.9)	8.6(2.1)
RBANS Coding	43.9(10.8)	47.0 (9.6)	43.6(9.1)	38.7(13.7)	34(10.7)
MMSE (Mean/SD)	28.6(1.6)	28.7(1.5)	28.8(1.3)	28.6(1.5)	27.6(1.7)

[1]Presented in detail by Ropacki et al P143

EPAD V500.0 $RBANS_{Total}$ By CDR and Amyloid Status



EPAD V500.0 Associations with Amyloid Positivity[1]

	Univariate Analysis			Multivariate Analysis[2]		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Age	**1.05**	**1.01 – 1.08**	**0.004**	**1.05**	**1.02 – 1.09**	**0.005**
$Gender_{male}$	1.38	0.93 – 2.04	0.11	1.25	0.82 – 1.90	0.30
Years of Education	0.98	0.93 – 1.04	0.54	1.01	0.95 – 1.07	0.74
Family History +	1.14	0.76 – 1.69	0.53	1.51	0.94 – 2.43	0.12
ApoEe4 +	**2.06**	**1.37 – 3.07**	**0.0004**	**2.10**	**1.37 – 3.23**	**0.0007**
CDR 0.5	**2.13**	**1.28 – 3.53**	**0.003**	**1.87**	**1.02 – 3.45**	**0.04**
$RBANS_{total}$	**0.98**	**0.96 – 0.99**	**0.005**	0.99	0.97 – 1.00	0.10

[1]Amyloid Positivity defined as CSF Aβ value <1,000pg/ml

[2]Adjusted for all other variables in the model i.e. age, gender, years of education, family history, ApoE status, CDR score and $RBANS_{total}$

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Optimal Algorithm for 'Predicting' Amyloid Positivity

CRITERIA	PPV	NPV
ApoEe4+ **AND** CDR=0.5 **AND** AGE >75	80%	65%
ApoEe4+ **AND** AGE >75	77.7%	60%
CDR=0.5 **AND** AGE > 75	60%	66.2%
ApoEe4 ONLY	45.2%	71.4%
CDR=0.5 ONLY	50%	68%
AGE > 75 ONLY	54.2%	67.3%

Caution: PPV and NPV affected by prevalence of condition in population – i.e. different parent cohorts will have different prevalence of amyloidosis

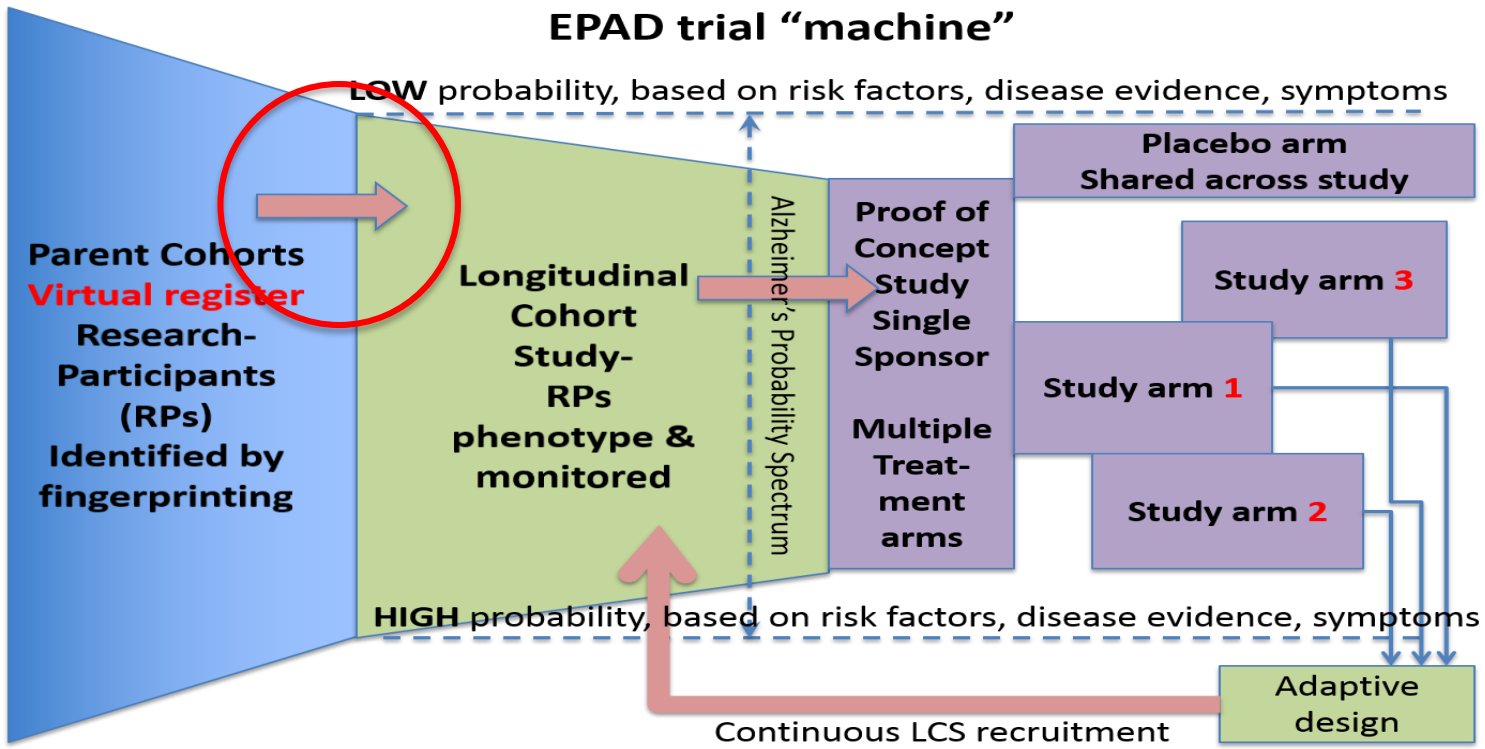
PPV = TP/(TP+FP)
NPV = TN/(TN+FN)

	Amyloid +	Amyloid -
Criteria +	True Positive	False Positive
Criteria -	False Negative	True Negative

EPAD V500.0 Summary (1)

- Optimal enrichment for trial readiness would be based on knowledge of:
  - ApoE status
  - Clinical populations
  - Age

- Analysis ongoing on optimal PPV algorithm including age bands and family history



EPAD V500.0 Summary (2)

- Data release to consortium due December 2018
  - P100 Vermunt Study enrolment from parent cohorts
  - P143 Ropacki Cognitive data summary
  - P165 Stirland Amyloid Status and Co-morbidities
  - LBP54 Bauermeister Psychometric Methodologies (DPUK)
  - OC38 Ritchie V500.0 Presentation

  Imaging analysis ongoing within VUMC under Prof Barkhof leadership of EPAD Imaging SAG

- V500.0 **global** release summer 2019
- V500.1 consortium release December 2019
- V1500.0 consortium release summer 2019
  - (presentations CTAD San Diego)

- EPAD Longitudinal Cohort Study Recruitment improving month by month
- EPAD Proof of Concept Trial (3 interventions) will start 2019/20

Acknowledgements

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