

Le Projet EPAD: European Prevention of Alzheimer's Dementia

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Disclosures

- I have no disclosures relevant to this presentation.

Overview of Presentation

- Background to the European Prevention of Alzheimer's Dementia (EPAD) Project
- The EPAD Model of Parent Cohort to EPAD Cohort (LCS)
- PREVENT an Exemplar of a Parent Cohort in the UK.
- The EPAD LCS Protocol
- The EPAD 'Balancing' Process

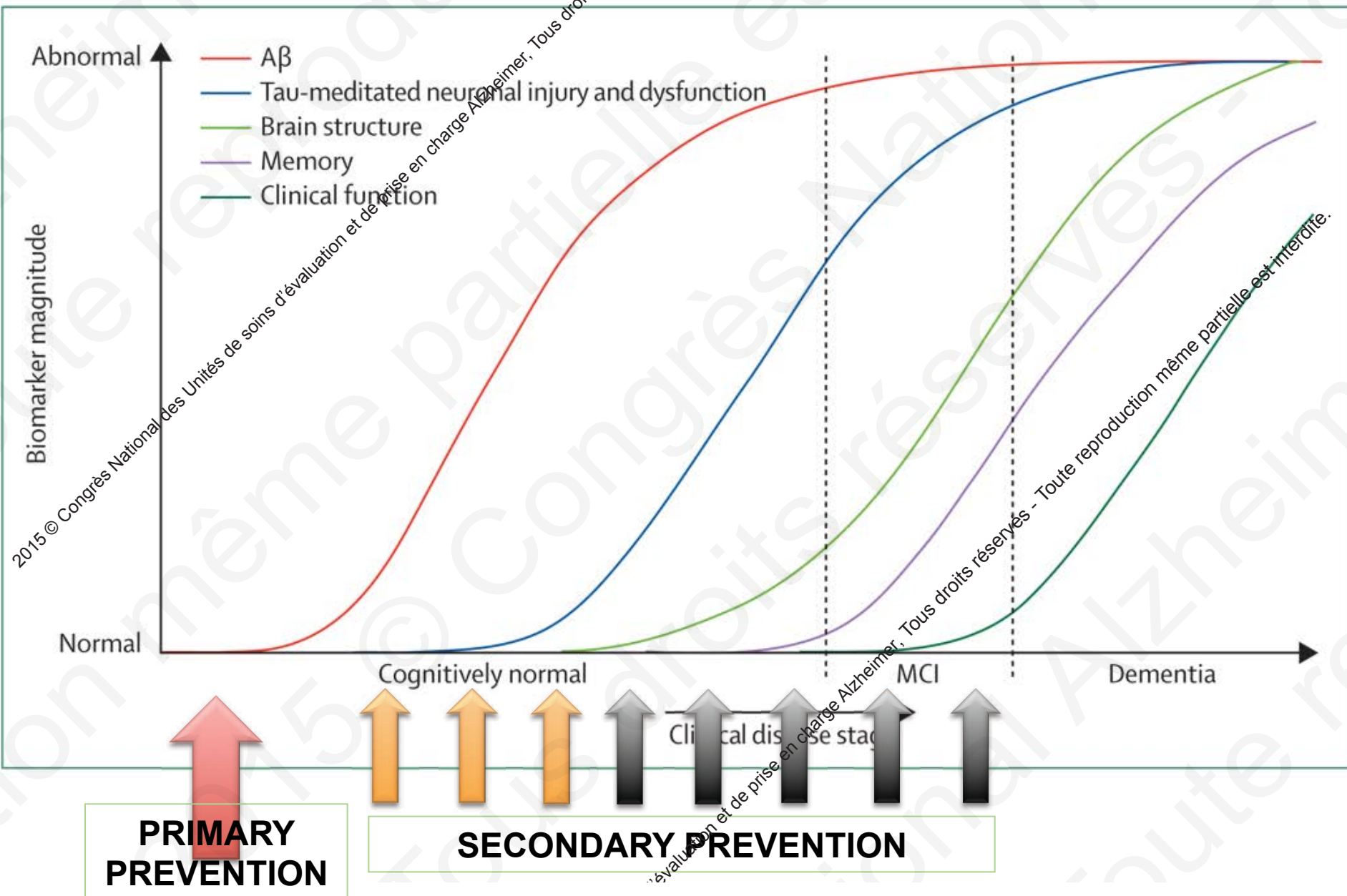


European Prevention of Alzheimer's Dementia (EPAD) Goal

The European Prevention of Alzheimer's Dementia (EPAD) project aims to develop an infrastructure that efficiently enables the undertaking of adaptive, multi-arm Proof of Concept studies for early and accurate decisions on the ongoing development of drug candidates or drug combinations for the prevention of AD dementia.



PREVENTION PREMISED ON UNDERSTANDING DISEASE BEFORE DEMENTIA





EPAD Consortium

EFPIA



SMEs



Patient Organisation



Academia

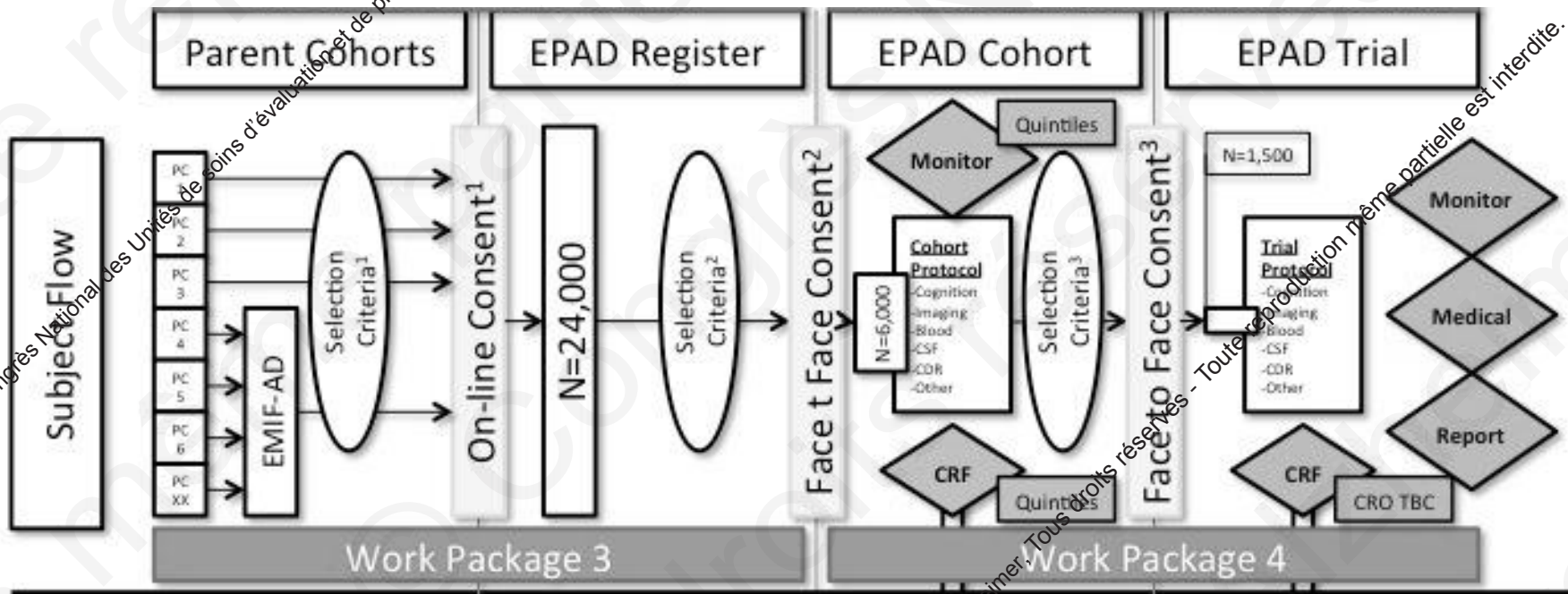


Other Industry





EPAD funnell





Selection of Research Participants

- Access data in Parent Cohorts
- Run Participant Discovery Software (EMIF)
- Generate list to Parent Cohort Owner who invite potential participants to attend local EPAD TDC.
- Parent Cohort Engagement ongoing





Parent cohorts from Scandinavia



Partner:
GEDOC and
SNAC-K

Miia Kivipelto/ Laura
Fratiglioni

External partners:
FINGER
CAIDE
DDRC
Register Oslo cohort

Miia Kivipelto
Miia Kivipelto
Steen Hasselbalch
Nenad Bogdanovic





Parent cohorts from Benelux



Partner:
Amsterdam

Philip Scheltens

External partner:
Antwerp

Sebastian Engelborghs





Parent cohorts from France



Partner:
Toulouse

Bruno Vellas

External potential partners:

Bordeaux
Lille
Lyon
Montpellier
Nantes
Paris Sud
Rennes

Dijon
Limoges
Marseille
Nancy
Paris Broca
Paris Nord
Strasbourg





Parent cohorts from Spain/Portugal



Partner

ALFA (BBRC)/IDIBAPS

José Luis Molinuevo

External partners

CITA

Pablo Martínez-Lage

Fundacion Reina Sofia

Miguel Medina

Sant Pau

Alberto Lleó

Coimbra

Catarina Oliveira

Lisbon

Alexandre de Mendonça





Potential parent cohorts ... Switzerland



Partner:
Geneva

Panteleimon
Giannakopoulos

External partners:
Zurich

Christoph Hoek/
Anton Giet

Lausanne cohort 65+

Brigitte Santos-
Eggmann

Bus Sante
MentDis_ICF65+
Colaas/PsyCoLaus

Idris Guessous
Alessandra Canuto
Martin Preisig





Parent cohorts from Italy



Partner:
ADWIBO Brescia

Giovanni B Frisoni/
Cristina Muscio

External partners:
InChianti
ILSA

Luigi Ferrucci
Emanuele Scafato





Parent cohorts from UK/Ireland



Partners:

PREVENT
Generation Scotland
UK Biobank
DCR

Craig Ritchie
David Porteous
Cathie Sudlow
Simon Lovestone

Numerous DPUK Cohorts





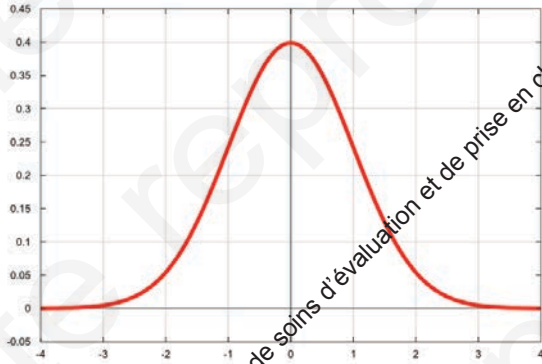
Finding and filtering for EPAD LCS

- EPAD LCS is the gateway into the EPAD Project for the Research Participants
- We need to make sure that the LCS population is fit for purpose
- We do this by looking for data that defines the most suitable people from the parent cohorts for EPAD

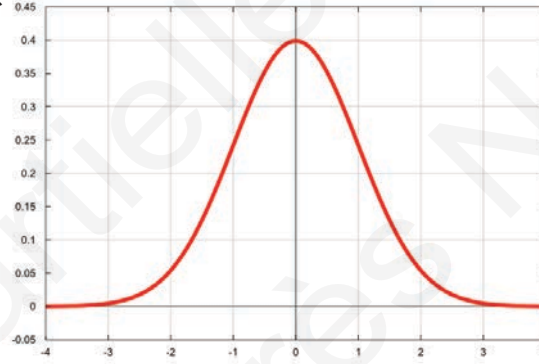




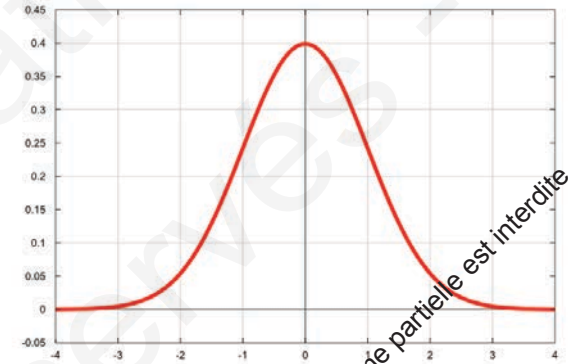
Finding the right participants



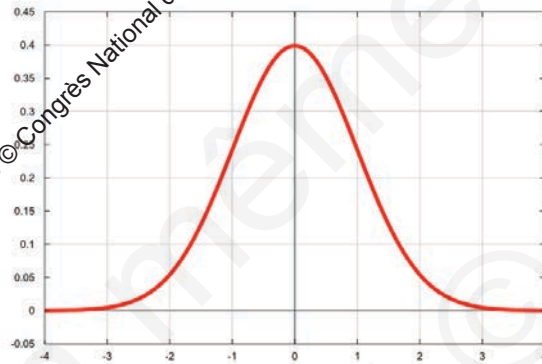
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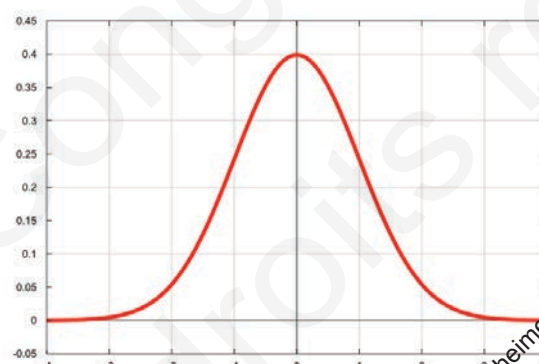
Aβ (Δ)



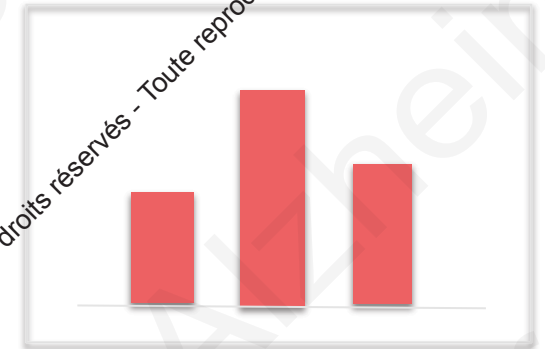
Tau (Δ)



Hippocampal Volume (Δ)



Episodic Memory (Δ)

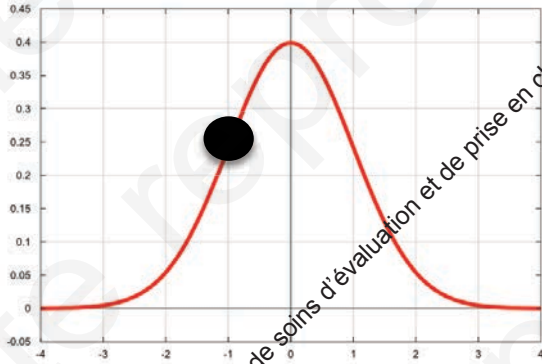


ApoEε4 status

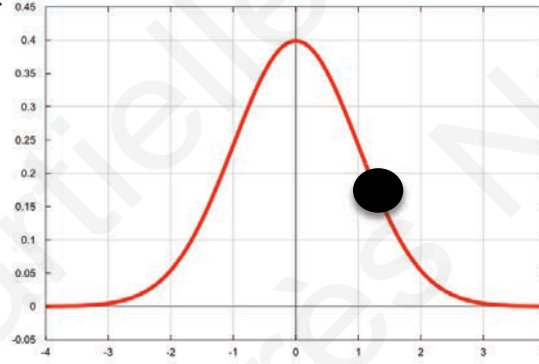




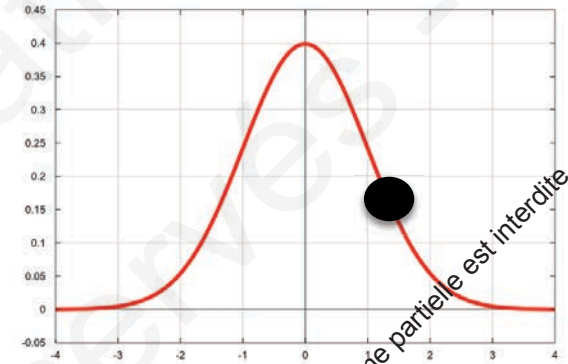
Finding the right participants



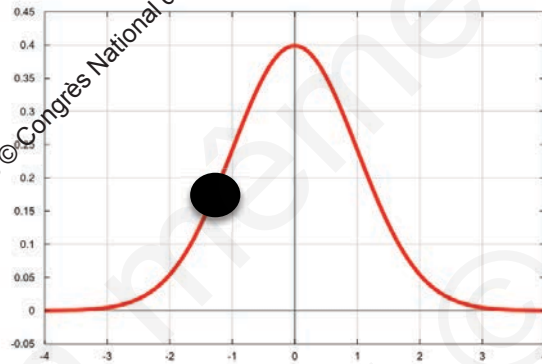
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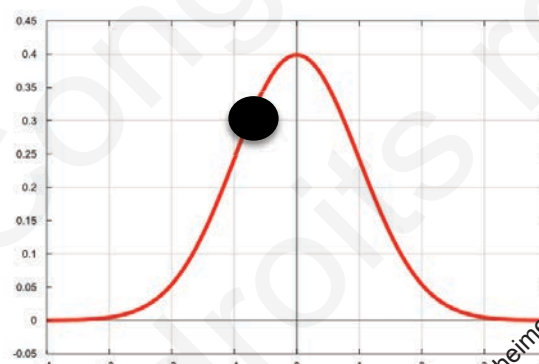
$A\beta$ (Δ)



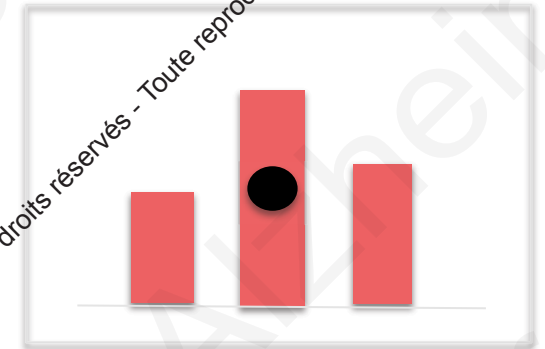
Tau (Δ)



Hippocampal Volume (Δ)



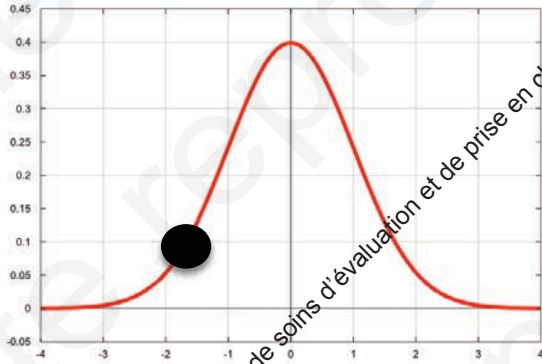
Episodic Memory (Δ)



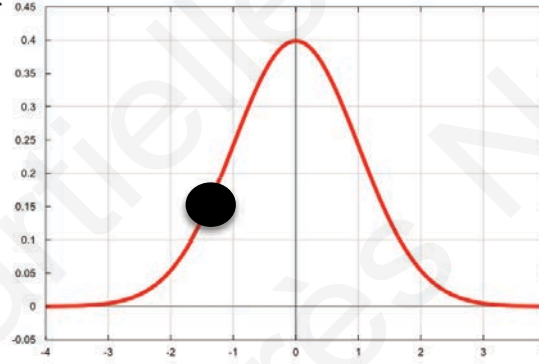
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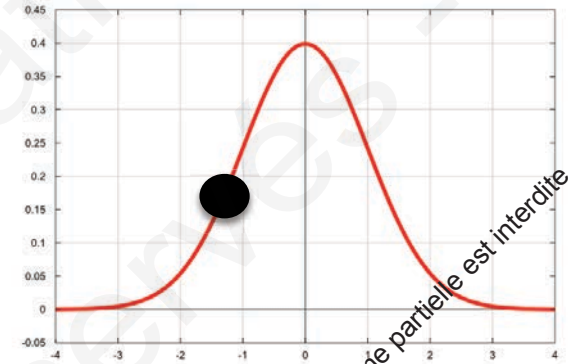
Pre-screening the wrong participants



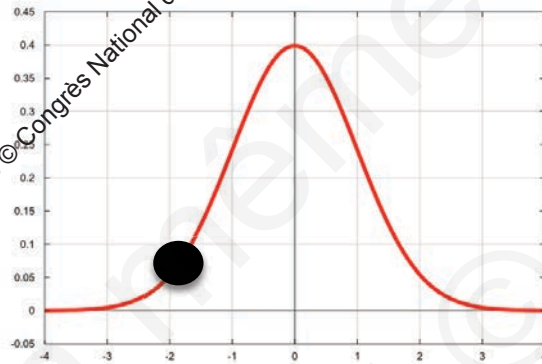
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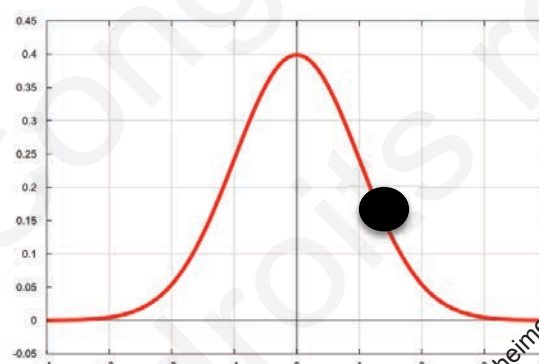
$A\beta$ (Δ)



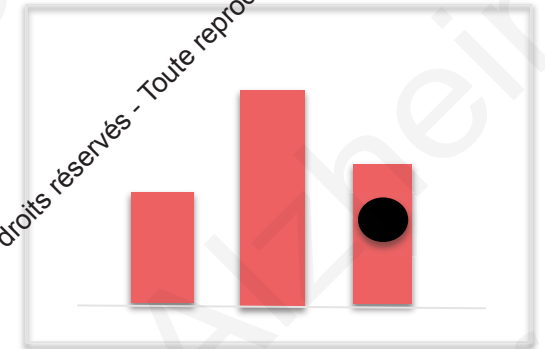
Tau (Δ)



Hippocampal Volume (Δ)



Episodic Memory (Δ)

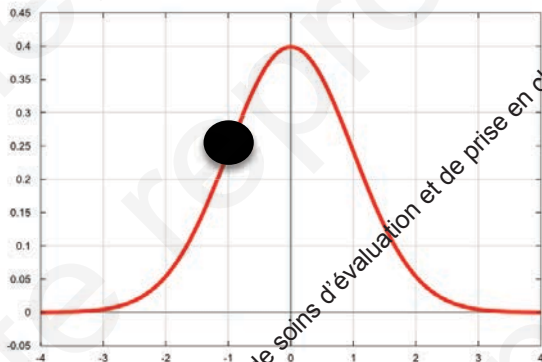


ApoE ϵ 4 status



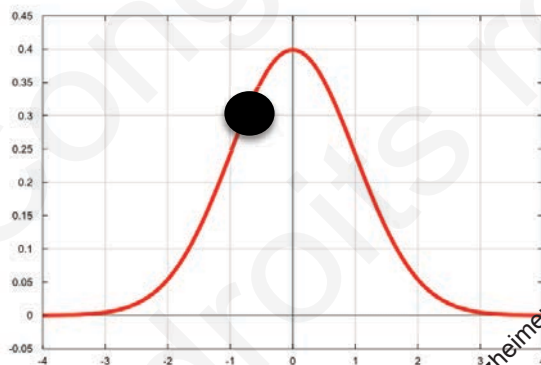


Retained uncertainty



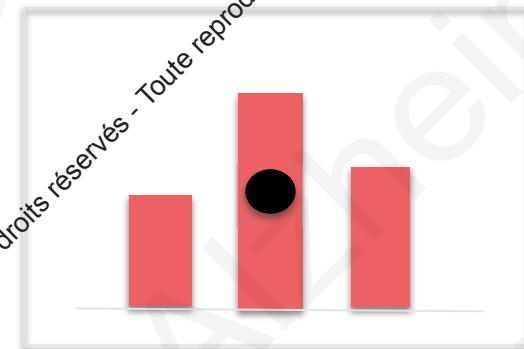
Age

Hippocampal Volume (Δ)



$A\beta$ (Δ)

Episodic Memory (Δ)



Tau (Δ)

ApoE ϵ 4 status



Research Programme

PREVENT

Imperial College
London

West London
Mental Health
NHS Trust

UNIVERSITY OF
CAMBRIDGE

UNIVERSITY OF
EXETER

KING'S
College
LONDON

Inserm
Institut national
de la santé et de la recherche médicale



Alzheimer's
Society
Leading the
fight against
dementia

UNIVERSITY OF
OXFORD

The PREVENT Programme:

- Aged 40-59
- Longitudinal cohort (Baseline and Year 2)
- Pilot phase (n=212)
- Edinburgh Site Recruitment (n=10)
- Oxford and Cambridge Site to open in 2016
- Target 700 participants by end 2016

Risk Factors Captured in PREVENT

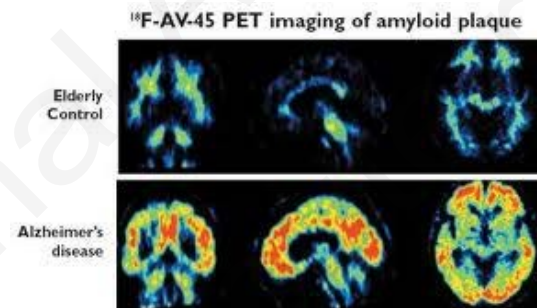
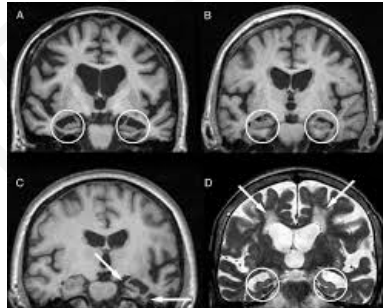
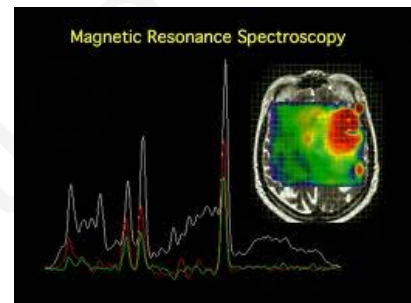
Domain	Risk	Measure being used
Principal Risk Model	ApoE genotype	Genetic analysis
	Parental history	History from participant
Genetic	Genotype	e.g. Genome Wide Association Studies
Environmental	Diet	Scottish Food Frequency questionnaire (Scottish Collaborative Group, 2004)
	Life Events	Life Stressor Checklist - revised (Wolfe & Kimerling, 1997)
	Sleep*	Pittsburgh Sleep Evaluation (Buysse et al., 1989)
	Exercise	Study Proforma
Clinical	Head Injury	BISQ (Brain injury screening questionnaire, 2011)
	Inflammation**	Inflammatory Markers
	Cardiovascular	ECG/Pulse & BP
	Depression*	CES-D (Radloff, 1977)
	Respiratory	Spirometry
	Stress	Salivary Cortisol / Resilience Questionnaire (Connor & Davidson, 2001)
	Diabetes / renal function / Metabolic Syndrome	Standard haematology and biochemistry.

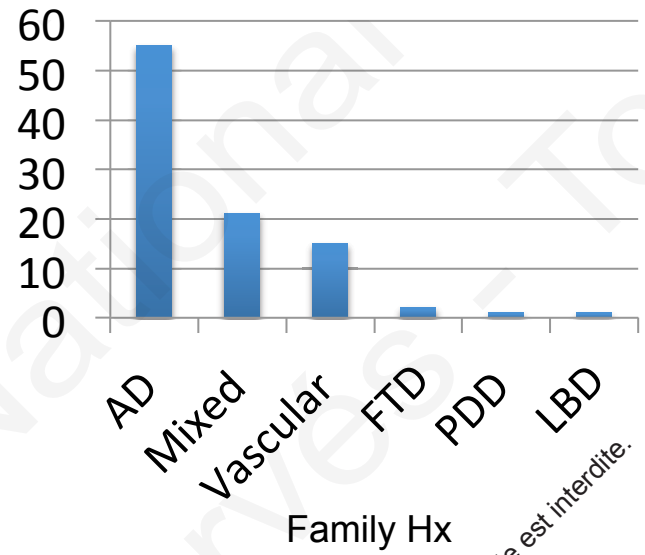
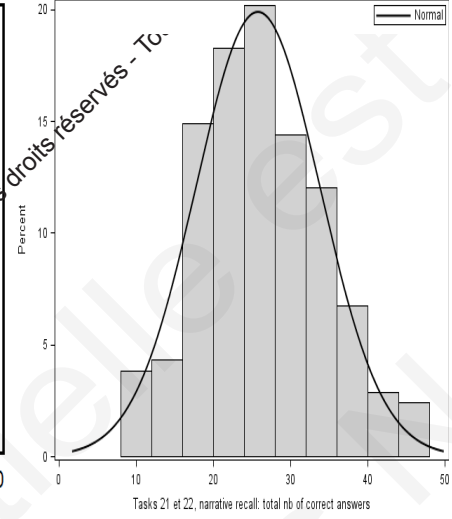
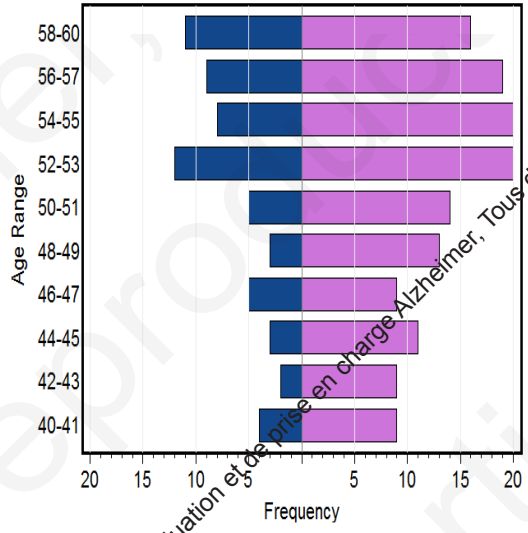
* May act as both risk for neurodegenerative disease and an outcome.

** May act as a risk factor for neurodegenerative disease and an expression of a core disease pathway.

Expressions of disease state in PREVENT Programme: Genes, biomarkers, cognition and language

- Imaging
 - fMRI with task, Magnetic Resonance Spectroscopy, Diffusion Tensor Imaging, WMRI, WML volume
 - Amyloid PET imaging via UKDP
- Cerebrospinal Fluid (30%)
 - A β /Tau (Discovery)
- Blood
 - A β , inflammatory markers, trace metals, micronutrients, lipids (Discovery)
- Saliva
 - Cortisol
- Cognition: COGNITO, Verbal Short Term Memory Binding Paradigm





Imperial College London

West London Mental Health NHS Trust

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Alzheimer's Society Leading the fight against dementia

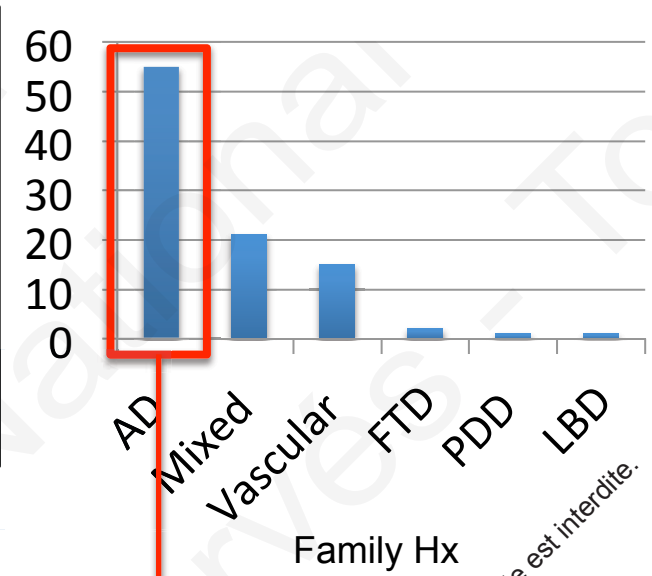
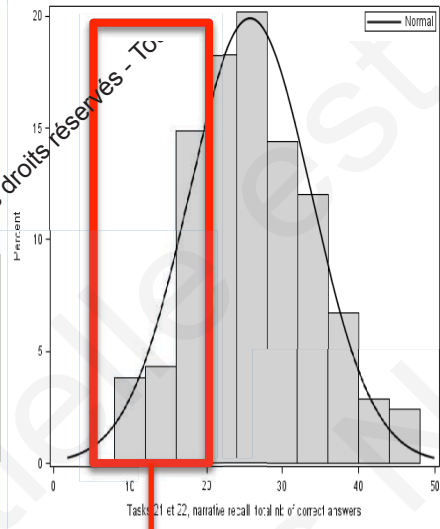
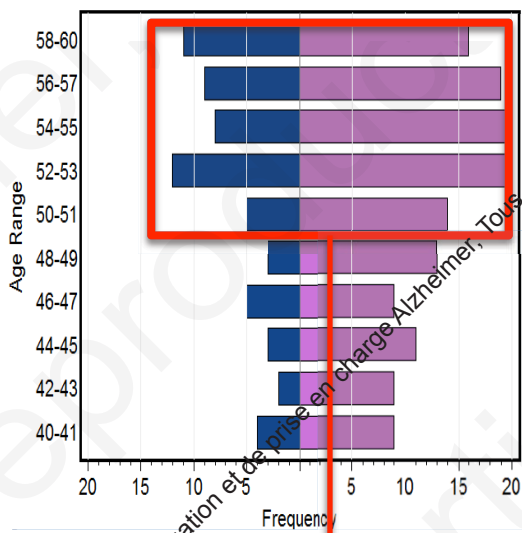
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Trial Delivery Centre

Consent

EPAD Cohort

évaluation et de prise en charge Alzheimer, Tous droits réservés - Toute reproduction même partielle est interdite.



Imperial College London

West London Mental Health NHS Trust

UNIVERSITY OF CAMBRIDGE

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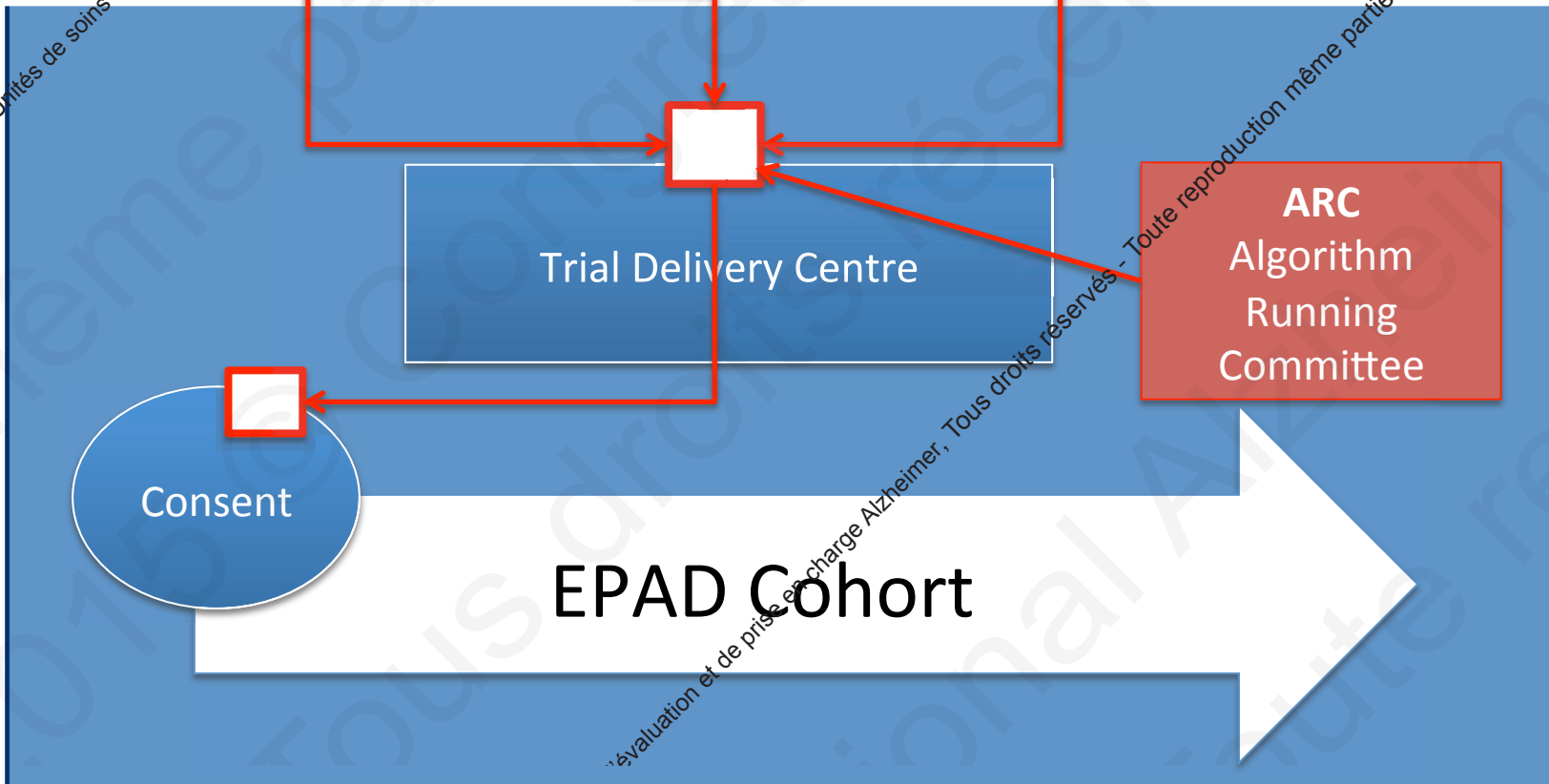
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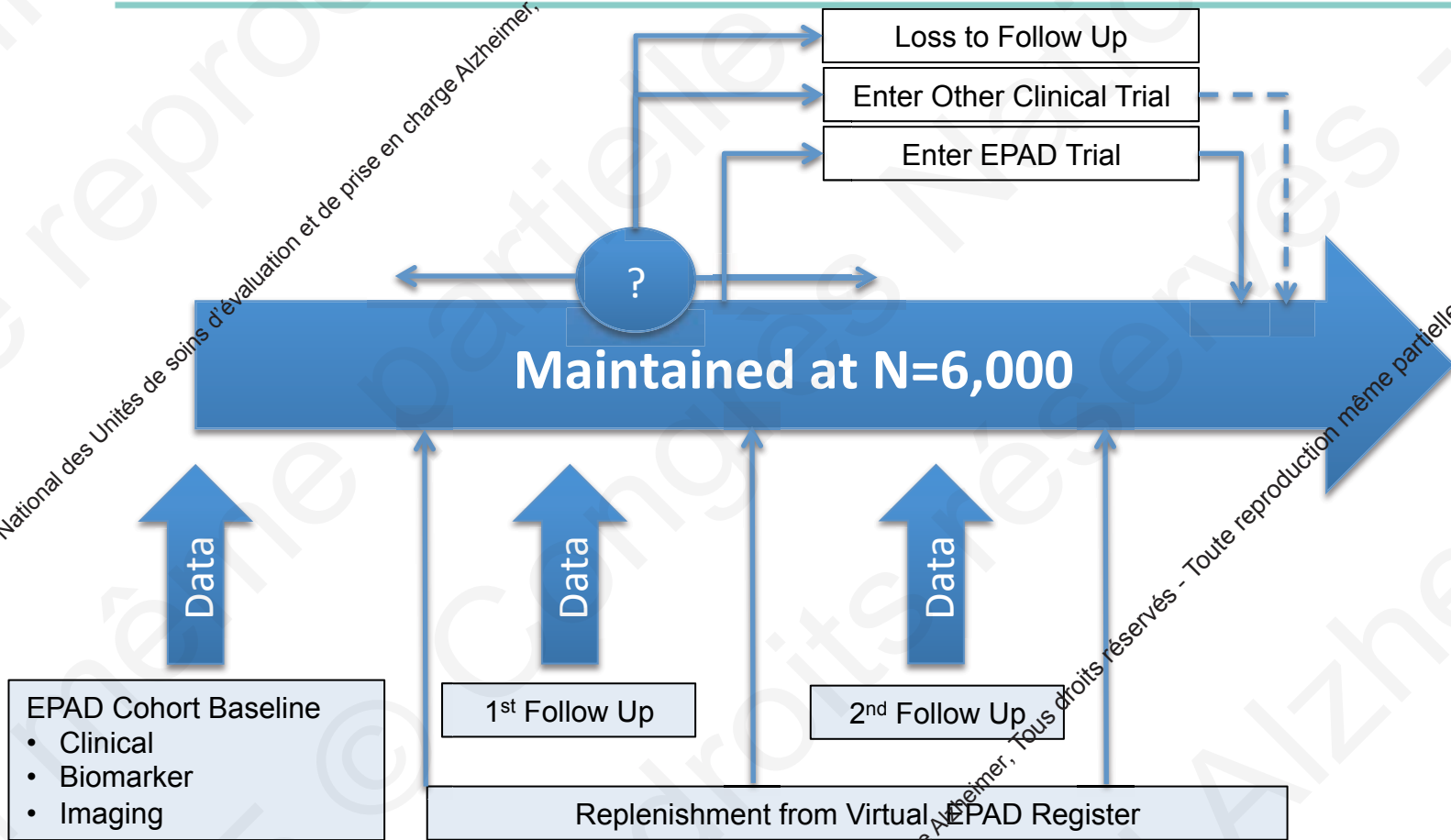
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EPAD Cohort

évaluation et de prise en charge Alzheimer. Tous droits réservés - Toute reproduction même partielle est interdite.

The EPAD Longitudinal Cohort Study





The EPAD LCS Protocol

- Annual assessments
 - 6/12 Cognition Assessment
- EPAD Neuropsychological Evaluation (ENE)*
- Neuroimaging*
- 100% will give CSF Sample for A β /Tau (Gothenburg)
- Blood, urine and saliva for genomics (blood) and storage for exploratory biomarkers (Edinburgh)
- Safety labs done locally at the TDCs
- Clinical and other risk factors



Cognition (in order of administration)

RBANS (Primary)

- 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

Four Mountains Task - (allocentric space; **Exploratory**)

Dot counting - (working memory; **Secondary**)

Flanker - (choice reaction time and set-shifting; **Secondary**)

Name/Face pairs - (paired associate learning; **Secondary**)

Supermarket Trolley Virtual Reality - (egocentric space; **Exploratory**)



Neuroimaging outcomes

Structural MRI

- Cortical thickness, deep GM 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 (DMN) & relation with hippocampal activity (rsfMRI)
- Bolus arrival time (multi-delay ASL)
- Network analysis (rsfMRI)

PET Amyloid Imaging

- To be confirmed in IMI2



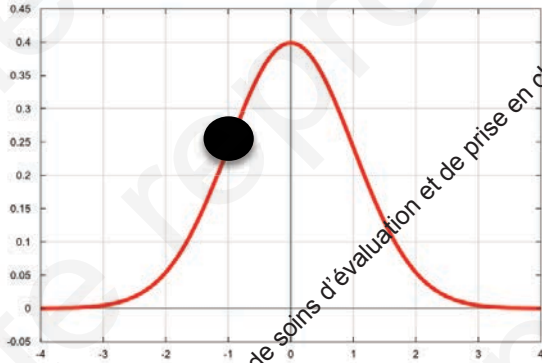


Do we have the right participants?

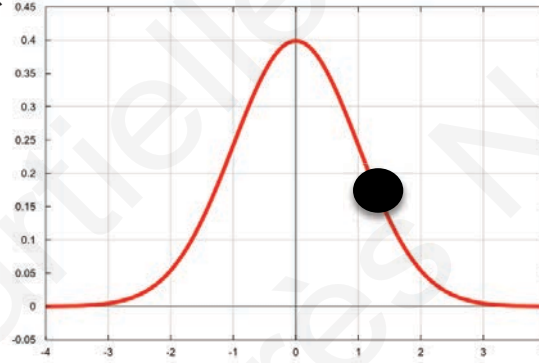
- Monthly review and reporting of the balance of probability and key variables in EPAD LCS.
- Driving forces:
 - The PoC trials in the virtual pipeline
 - The ability to model on disease and within disease decline in the primary outcome



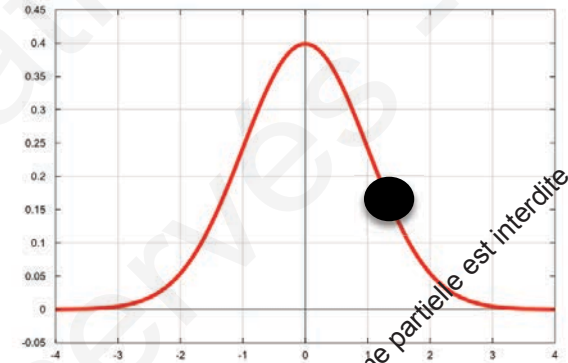
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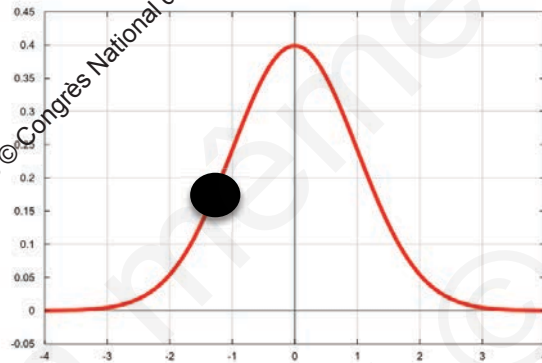
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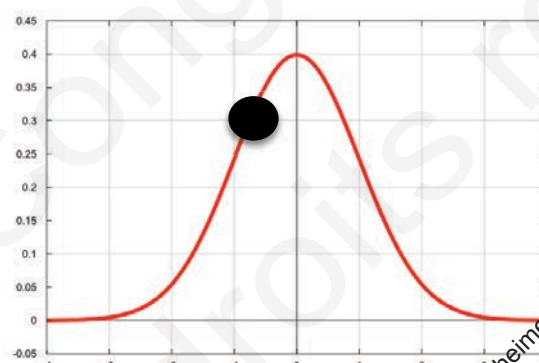
$A\beta$ (Δ)



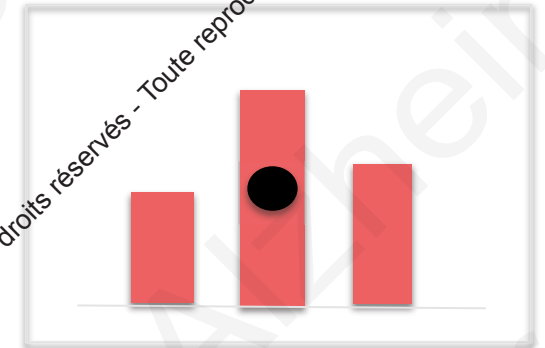
Tau (Δ)



Hippocampal Volume (Δ)



Episodic Memory (Δ)



ApoE ϵ 4 status



Report 1: Trajectory Report

- Using initial disease model every individual will be given a %probability of being:
 - Decliner
 - Stable
 - Improver
- To a range of potential outcomes

Report 2: Traditional Categories

- Proportion Amyloid + (can alter thresholds)
- Proportions fulfilling inclusion criteria for PoC in pipeline

Report 3: Bespoke Reports

- e.g. Responsive to queries from CCSC (Feasibility Analysis)
-



Responses to Report

- Tools to balance and influence cohort constitution:
 1. Change variables in or parameters around the algorithms.
 - Accuracy of different algorithms will be tested within programme for ability to identify desired individuals.
 2. Under/over sample from parent cohorts (all will have inherent characteristics in their sample)
 3. De-select LCS Research Participants before M12 visit.





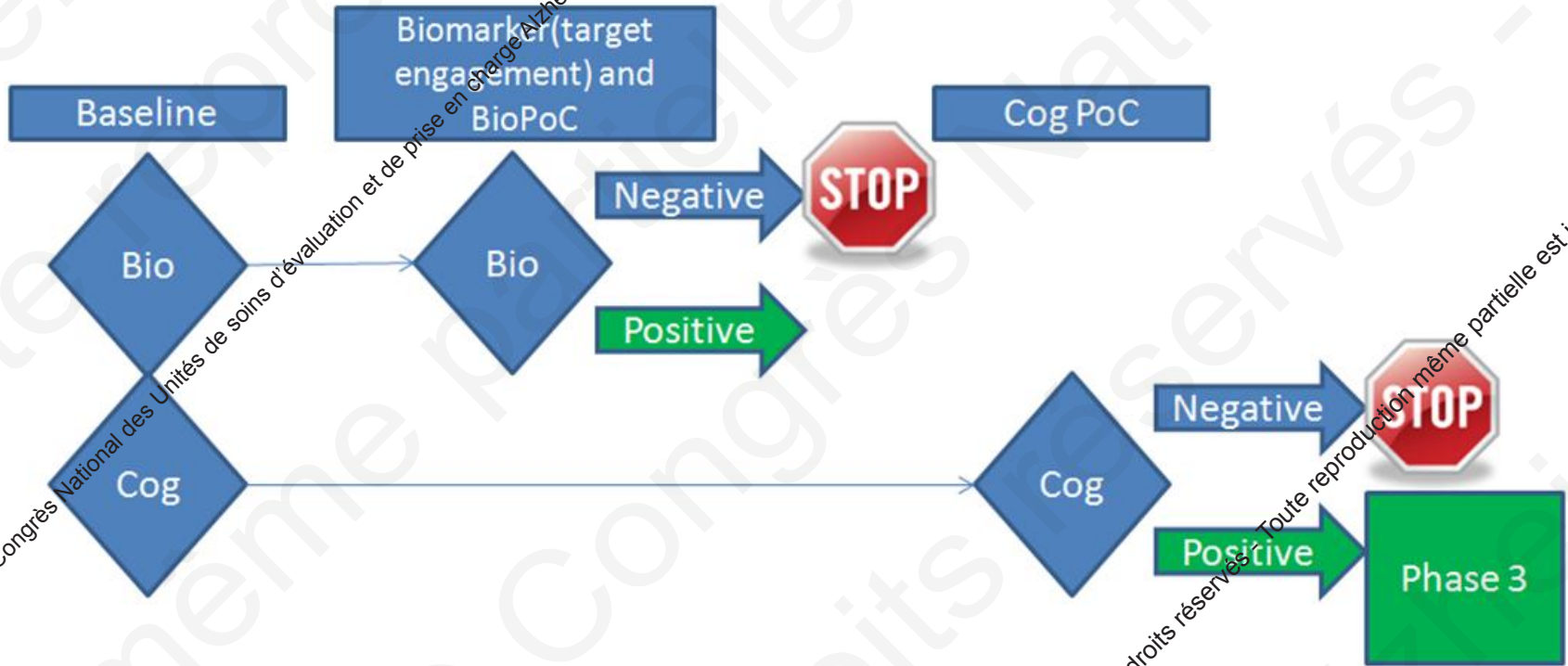
From EPAD Cohort to PoC Trial

- 1,500 participants at any one time enter the PoC study.
- Standing 'master' protocol with appendices reflecting different arms.
- Primary outcome is cognition
- Intermediate phenotype is biomarker reflecting drug target





The EPAD PoC Trial



Allows early decisions on progression to longer term clinical outcomes by impact on pre-defined and target-specific intermediary phenotype.





Conclusions

- April 1st expect First Research Participant to be Recruited into EPAD Longitudinal Cohort Study.
 - Success of project predicated on close academic collaboration with Parent Cohorts across Europe and engagement with public on the vision of EPAD
 - Forming a key part of the developing global network of aligning projects:
 - GAP, CPAD, JPAD and APAD
-
-



Acknowledgements

National Leads

Ritchie/Gallacher - UK & Ireland

Miia Kivipelto - Scandinavia

José Luis Molinuevo – Spain/Portugal

Philip Scheltens - Benelux

Giovanni Frisoni - Switzerland/Italy

Bruno Vellas - France

Executive Committee & PMO

Serge Van der Geypen (JPNV)

Luc Truyen (JPNV)

Andrew Satlin (Eisai)

Craig Ritchie (UEDIN)

Simon Lovestone (UOXF)

José Luis Molinuevo (BBRC)

Carlos Díaz (Project Manager)

Sandra Pla (member of PMO)

Lennert Steukers (member of PMO)

Mila Etlropolski (JPNV – member of PMO)

Judi Syson (UEDIN – member of PMO)

Work Package Leads

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Andrew Satlin (Eisai)

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WP2

Adrian Mander (MRC)

Shobha Dhadda (Eisai)

Scott Berry (BERRY)

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Gerald Luscan (Pfizer)

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Catherine Debove (BI)

Miia Kivipelto (KI)

Mila Etlropolski (JPNV)

WP5

Carlos Díaz (SYNAPSE)

Serge Van der Geypen (JPNV)

WP6

Jean Georges (AE)

Sean Knox (NOV)

WP7

José Luis Molinuevo (BBRC)

Frank Tennigkeit (UCB)

Saira Ramasastry (SYNAPSE)

WP8

Edo Richard (RUMC)

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Shirlene Badger (UCAM)

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