European Prevention of Alzheimer’s Dementia (EPAD)

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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.
Vision of EPAD

• To establish a global standing trial-ready platform which is projected to reduce clinical testing cycle times by two years or more and achieve greater efficiency and uniformity in trial populations through large, well-characterized trial-ready cohorts, certified clinical trial sites, and an adaptive POC trial mechanism

• This platform will enable the delivery of efficient and effective proof of concept and confirmatory trials and ultimately the more rapid delivery of effective therapies to patients or those at risk
Enhancing and Speeding up Clinical Trials

Clinical Trial Infrastructure
- Offer network publicly- and industry-sponsored POC or Confirmatory trials
- Master Services Agreement
- Site rater certification
- National IRB
- Site Accreditation

Prospective Readiness Cohort Study
- No lag time for recruitment
- Significantly lower screen failure
- Diagnostic confidence
- Quality ‘run in’ data
- Test drive clinical end-points
- Research and validate biomarkers
- Amortize costs

Biomarker-rich Cognitive Endpoint Trials
- Offer platform for publicly- and industry-sponsored POC or Confirmatory trials
- Decrease risk/time; Improve decisions for Ph 3
- Develop protocol for Ph 2/3 global POC (EPAD, CPAD, etc.)
Secondary Prevention of AD

• **STEP 1: Identifying the ‘at risk’ person**
  – Risk factors (fixed and modifiable)
  – Cognitive profile (not ‘symptoms’)
  – Biomarker evidence of disease
  – Changes in these over time

• **STEP 2: Tailoring treatment**
  – Reducing modifiable risk factors
  – Enhancing resilience
  – Disease course modification through specific drug intervention(s)

• **STEP 3: Measuring success**
  – Individual’s probability status reduces
    • Cognition improves
    • Biomarkers normalise
    • Risk of dementia decreases
Stepped Approach

- Define criteria for identifying AD pathology early in the course of disease in people who have no or minimal symptoms
- EPAD Register: January 2016 (target n=24,000)
  - Identifying these individuals from existing population and clinical cohorts or registers
- EPAD Cohort: MAY 2016 (target n=6,000)
  - Developing a large longitudinal cohort study to ease identification for trial inclusion, provide trial run-in data and generate high quality data for updating AD disease models, including defining risk for developing AD and evaluating efficacy
- EPAD Trial: Q4 2017 (target n=1500)
  - Establishing a protocol and infrastructure for a standing, double-blind, adaptive, proof-of-concept clinical trial for secondary prevention of AD
Stepped Approach

Criteria for identifying AD pathology

Define criteria for identifying AD pathology early in the course of disease in people who have no or minimal symptoms

EPAD Register
N = ± 24,000

Identifying these individuals from existing population and clinical cohorts or registers.

EPAD Cohort
N = ± 6000

Developing a large longitudinal cohort study to ease identification for trial inclusion, provide trial run-in data and generate high quality data for updating AD disease models, including defining risk for developing AD and evaluating efficacy

EPAD Trial
N = ± 1500

Establishing a protocol and infrastructure for a standing, double-blind, adaptive, proof-of-concept clinical trial for secondary prevention of AD
EPAD Project Overview

EPAD trial “machine”

- LOW probability, based on risk factors, disease evidence, symptoms
- Placebo arm
  - Shared across study
- Parent Cohorts
  - Virtual register research
  - Participants (RPs)
  - Identified by fingerprinting
- Longitudinal Cohort Study
  - 6000 Research Participants
  - phenotype & monitored
- Proof of Concept Study
  - Single Sponsor
  - Multiple Treatment arms
- Study arm 1
  - 500 RPs
- Study arm 2
  - 500 RPs
- Study arm 3
  - 500 RPs
- Adaptive design
- Continuous LCS recruitment
- Alzheimer's Probability Spectrum

HIGH probability, based on risk factors, disease evidence, symptoms
The EPAD Cohort

Maintained at N=6,000

Draw through existing imaging (and other) data from Parent Cohort

EPAD Cohort Baseline
- Clinical
- New biomarker
- New imaging

Data

1st Follow Up

2nd Follow Up

Loss to Follow Up
Enter Other Clinical Trial
Enter EPAD Trial

Replenishment from EPAD Register
The EPAD PoC Trial

- Allows early decisions on progression to longer term clinical outcomes by impact on pre-defined and target-specific intermediary phenotype
- EPAD PoC trial budget is not covered by Innovative Medicines Initiative (IMI)
EPAD Adaptive Trial

Selection Criteria

Trial Cohort

Placebo

Tx #1

Tx #2

Tx #3

Tx #2 + #3

Adaptation by change in intermediate phenotype

Adaptation on cognition outcomes
Summary

EPAD is a recently started IMI project aiming to deliver a standing, double-blind, AD prevention PoC Adaptive Design trial which is sustainable beyond the 5 years of the Innovative Medicines Initiative funding.
THANK YOU
In principle, the cohort will have pre-dementia subjects with limited exclusion criteria (mainly people with other overt causes of cognitive impairment)

- It will include a trial ready population ranging from:
  - Normal cognitive people AD pathology biomarker negative (TBD)
  - Normal cognitive people AD pathology (biomarker) positive (TBD)
  - Prodromal AD/ MCI due to AD (TBD)

- For disease modelling this will be treated like a spectrum of single process
  - It will take into account additional info (ApoE genotype, ..)
In principle, the cohort will have limited exclusion criteria. Basic inclusion criteria

- Age 50 to 80
- Subjects able to read and write, ≥ 7 years of education
- Do not satisfy clinical criteria for any type of dementia
- Do not carry a PS1, PS2 or APP mutation
- Do not suffer from any neurological, mental, medical condition associated with risk of cognitive impairment or limiting psychometric testing
- Do not have any cancer or history of cancer in the preceding 5 years
- Are willing to participate in the EPAD PoC Trial subject to further informed consent
The baseline assessments will characterise:

- Biomarker (likely to include CSF Aβ42 and tau biomarkers)
- Imaging (MRI)
- Cognitive status (outcomes advised by WP1)
- PET amyloid in connection with IMI-2 call?

There will be a dynamic review of the ‘spectrum’ in the LCS (between WP4 and WP2) in a fashion that Scott Berry referred to as ‘managed heterogeneity’.

We predict annual follow up assessments:

- Cognitive follow
The EPAD Centre Network

• Each EPAD-TDC’s will be expected to recruit 200 participants to the EPAD Cohort and 50 of these people into the EPAD PoC Trial.

• EPAD-trial delivery centres network will be providing best practice to deliver the EPAD Cohort and PoC Trial.

• The development of the broader EPAD Community will assist with the ongoing motivation of staff and become a key element for sustainability beyond year 5 of the program.
**EPAD Neuropsychological Examination (ENE)**

- **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)
EPAD Neuroimaging Battery

**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**
CSF and Blood Biomarkers

- CSF Abeta and Tau
- Blood, urine and saliva for genomics (blood) and storage for exploratory biomarkers