Designing the EPAD (European Prevention of Alzheimer’s dementia) platform trial: Key issues

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(including material from Scott Berry and the entire EPAD project)

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www.ep-ad.org
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http://www.imi.europa.eu
Outline

- Alzheimer’s: Clinical trial trends/issues
- What is a platform trial (brief)?
- What is EPAD (setup)?
- LCS: Longitudinal cohort study
- POC: Proof of concept platform trial
- Why did no drugs enter the POC study?
Alzheimer’s trends and issues

- Prevalence: Increasing
- Treatment options (Europe): A few drugs with symptomatic effect
- Expensive care (nursing homes)
- Very high failure rate of drug candidates
- Early treatment: Current thinking says new treatments should be initiated before clinical symptoms =>
  1: Long trials; 2: Large trials; 3: Screening for high-risk subjects
- Cognition testing: Many dimensions. Low precision/resolution. Cannot discriminate between Alzheimer’s and other dementias
- Biomarkers: CSF (inconvenient) and PET (expensive) can show amyloid plaques

- Conclusion on operational aspects: Big trial machinery needed
What is a platform trial?

- “Trial infrastructure” ”Perpetual trial machine”
- Somewhere between a completely joint study and individual studies of several drugs
- Shared design in terms of operations, simplifying protocol writing; assessment schedule; protocol training; work at site; data management etc
- Separate study in terms of timelines and reporting (and allowing for specific features)
- Sharing of placebo subjects (reducing resources and allowing more subjects on active treatments)
What is EPAD?

- **European Prevention of Alzheimer’s Dementia** Consortium
- Joint project funded by EU (through IMI) and EFPIA partners
- 39 partners: 14 pharmaceutical companies; Academic institutions; companies (CROs, biomarkers, statistical expertise etc); patient organization
Study overview

- National cohorts (existing)
- Vague criteria
- EPAD Longitudinal cohort study (following untreated research participants; many assessments)
- Strict criteria (pre-Alzheimer’s)
- EPAD proof of concept study (randomised; multiple treatments)
Purpose:
To serve as feed-in study for POC study
To inform on disease progression in the pre-Alzheimer’s time period

Inclusion criteria:
Age
No Dementia

Assessments:
**APOE lipoprotein gene** (known Alzheimer’s risk factor)
**Cognition RBANS** (Repeatable Battery for the Assessment of Neuropsychology Status)
chosen to have good resolution in the pre-Alzheimer’s domain
**CSF samples** to test for tau and A-beta (Alzheimer’s brain plaque)

Subject numbers:
Original plan: 6000 – FSFV: May 2016
Study closure: 2094 – LSFV: March 2020
**Platform** means testing several treatments in a similar way

**Master protocol** describing platform supplemented with "appendices", each considering one sub-study

Each sub-study follows its own time-line – treatments come and go (which is why a platform trial is also called *infrastructure*)

**Major treatment case:** Drug (oral) or biological (injection)

May present as one treatment arm or several (example: doses; frequency)
The proof-of-concept study – compounds

- Compound owner applies to the compound selection committee
- Detailed information on the compound is confidential
- Compound has shown *proof-of-principle* (exceptions possible)
- Sample size and duration (up to 4 years) decided by committee based on owner input
The proof-of-concept study

- **Master** common protocol covering all interventions
- **Inclusion criteria**: Subject in longitudinal study for at least 6 months
- CSF sample showing signs of plaque buildup
  \( (\text{A}\beta \ 1-42 < 1000 \  \text{pg/ml}) \)
- Non-demented (CDR < 1)
- Age > 50 years
- Study partner

- **Stratification:**
  - APOE gene
  - RBANS (with cognitive impairment: "prodromal"; without: "preclinical")
  - A sub-study can select among the 4 strata

- **Logistics:**
  - Patients satisfying the inclusion criteria will be randomized to one of the sub-studies "appendices"
Appendices (trial in a trial)

- **Purpose:** To test a single treatment within the POC study
- **Treatment:** Oral (like daily) or Injection (like monthly) or …
- **Inclusion criteria:** one or more of the strata
- Potentially, sub-study specific criteria
- **Blinding:** Treatment blinded; sub-study not blinded
- **Randomization:** 1/4 placebo; rest is company choice (3/4 on a single dose; or 1/4 on each of three doses)
- Treatment period up to 4 years
Primary endpoint: RBANS – Assessed every 6 months

- Disease progression model for measuring the change in the rate of decline over time for a treatment compared to control arm

\[
Y_{ij} = \begin{cases} 
\gamma_i + \sum^{\alpha_j \in \{-1, 0, 1\}}^{-1} \alpha_j + \epsilon_{ij} & j = \ldots, -2, -1 \\
\gamma_i + \epsilon_{ij} & j = 0 \\
\gamma_i + \exp(\theta_{ij}) \sum^{-1} \alpha_j + \epsilon_{ij} & j = 1, 2, 3 \ldots 
\end{cases}
\]

Common Treatment Effect:
Disease Progression Ratio (=1 is control)

Control Arm Model:
Stratified by Subgroup
\(\alpha_{-2}, \alpha_{-1}, \alpha_1, \alpha_2, \ldots\)
Subjects: Individual assessment each 6 months
Compounds: Interim analysis each 3 months. One analysis per substudy

Decisions require 50 subjects for 12 months in substudy. Subjects included if in relevant substudy or placebo in parallel substudy (same strata; within time-window of relevant study)

Futility: Prob (CPRR < 0.90) < 0.05
Stop substudy

Efficacy (called "graduation": treatment ready for phase III): Prob (CPRR < 0.90) > 0.85
Stop for enrolment – Possible continuation of subjects already included

Performance evaluated by simulation
What is unique about EPAD?

- Efficiency (general for platform trials):
  - Operational efficiency due to shared design
  - Shared placebo group

- Recruitment (only EPAD):
  - Continuous availability of enriched pre-Alzheimer’s subject population
  - Detailed information at least 6 months pre-trial
Why did no drugs enter the POC study (speculation)?

- Longitudinal cohort study:
  - Too slow to start and too slow to recruit, making it a bottleneck for recruitment

- Risk and trust:
  - Can the trial deliver? Particularly an issue for the first drug
  - Primary endpoint (RBANS cognition): Limited experience
  - Lack of control (Sponsor > Consortium > CRO > Site)
  - Simultaneous development outside trial: Increased focus on the failure rate of drugs developed for preventing Alzheimer’s
Contact information

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- The Statistical Analysis Plan is available at
  - http://ep-ad.org/about/publications/
- Pick project deliverables  -> WP2
- And then it is listed as 2.11.