EPAD
European Prevention of
Alzheimer's Dementia Consortium

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

Philip Hougaard (Lundbeck)

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

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- http://www.imi.europa.eu

EPAD
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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?

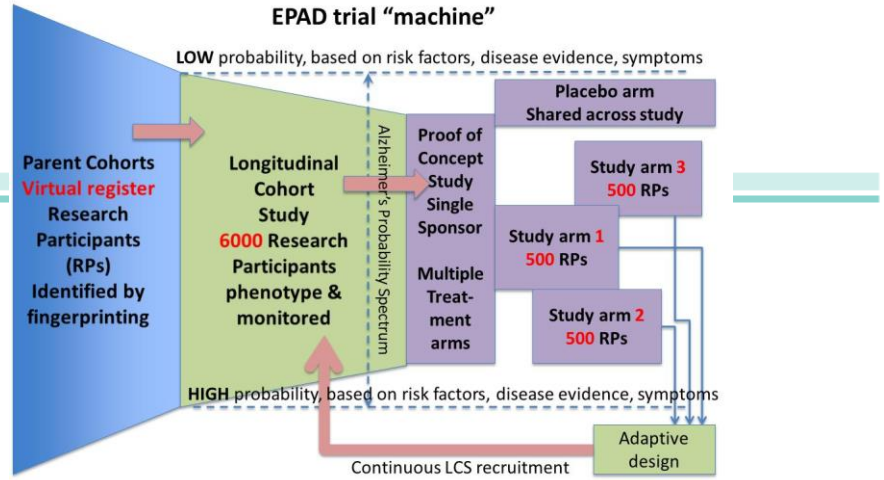
- ”Trial infrastructure” ”Perpetual trial machine”
- Somewhere between a completely joint study and individual studies of several drugs
- Shared design in terms of operations, simplifying protocol writing; assessment schedule; protocol training; work at site; data management etc
- Separate study in terms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

EPAD
European Prevention of Alzheimer's Dementia Consortium

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
- Global Assembly: 2015 Edinburgh; 2016 Barcelona; 2017 Stockholm; 2018 Amsterdam; 2019 Geneva; 2020 Virtual

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)

Longitudinal cohort study

- **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

The proof-of-concept study – platform trial

- ***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***)

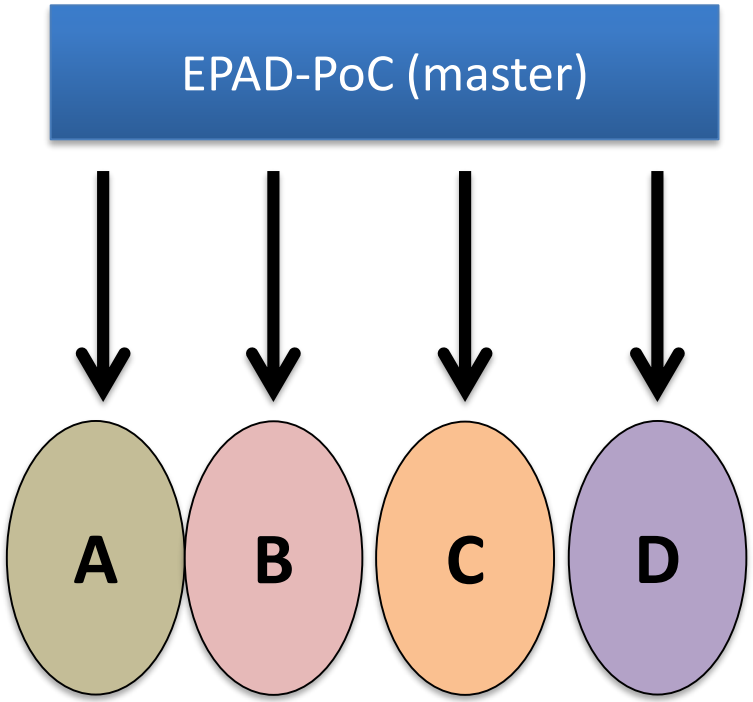
- **Major treatment case:** Drug (oral) or biological (injection)
- May present as one treatment arm or several (example: doses; frequency)

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 (Aβ 1-42 < 1000 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)

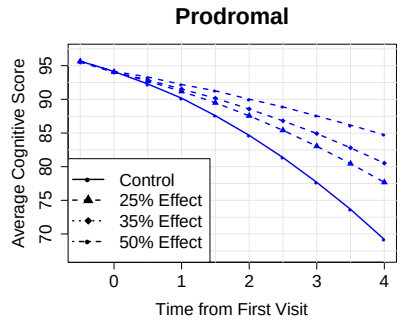
- **Purpose:** To test a single treatment within the POC study
- **Treatment:** Oral (like daily) or Injection (like monthly) or …
- **Inclusion criteria:** one or more of the strata
- Potentially, sub-study specific criteria
- **Blinding:** Treatment blinded; sub-study not blinded
- **Randomization:** 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

Statistical analysis

- 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

$$Y_{ij} = \begin{cases} \gamma_i + \sum_{v=j}^{-1} \alpha_v + \epsilon_{ij} & j = \cdots, -2, -1 \\ \gamma_i + \epsilon_{ij} & j = 0 \\ \gamma_i + \exp(\theta_{t_i}) \sum_{v=1}^{j} \alpha_v + \epsilon_{ij} & j = 1,2,3 \ldots \end{cases}$$

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



Control Arm Model:
Stratified by
Subgroup
$\alpha_{-2}, \alpha_{-1}, \alpha_1, \alpha_2, \ldots$

Ongoing decision making

- 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 sub-study 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

- Philip Hougaard
- Biometrics, Lundbeck, Denmark
- phou@lundbeck.com

- 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.