EPAD: The European Prevention of Alzheimer's Dementia platform trial

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

Alzheimer's trends and issues

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 subjects at high risk for Alzheimer's
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
Implies: Big trial machinery needed

Study overview

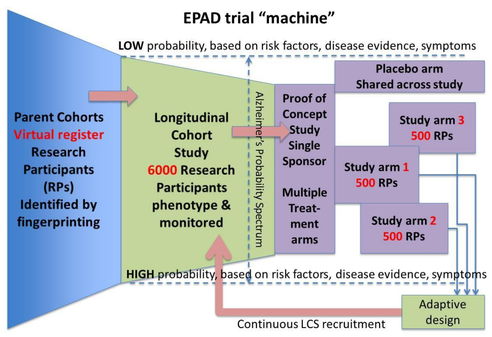
National cohorts (existing)

↓ Vague criteria

EPAD Longitudinal cohort study (following untreated research participants; many assessments)

↓ Strict criteria

EPAD proof of concept study (randomized; multiple treatments)



Ongoing decision making

Interim analysis each 3 months.
One analysis per sub-study
Bayesian model for CPRR (Cognitive Progression Rate Ratio)
Futility: Prob (CPRR < 0.90) < 0.05
Stop sub-study
Efficacy (called "graduation": treatment ready for phase III)
Prob (CPRR < 0.90) > 0.85
Stop for enrolment - Possible continuation of subjects already included

What is a platform trial? And what is EPAD?

"Trial infrastructure"
Between a joint study and separate studies
Shared design leading to operational efficiencies
Separate studies in terms of timelines and reporting ("sub-studies")
Sharing of placebo subjects (reducing resources)

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

Longitudinal cohort study

Purpose:
To serve as feed-in for POC study
To inform on disease progression in the pre-Alzheimer's time period
Timing:
FSFV: May 2016
LSFV: March 2020
Subject numbers:
Original plan: 6000
Actual: 2094

Advantages of the EPAD platform trial

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

References

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

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The proof-of-concept study – platform trial

Master protocol covering all interventions
Supplemented with "appendices", each considering one sub-study
Inclusion criteria: Subject in longitudinal cohort study for at least 6 months
CSF sample showing signs of plaque build-up
Age > 50 years; Non-demented
Endpoint (cognition): RBANS (Repeatable Battery for the Assessment of Neuropsychology Status)

Potential reasons that no drugs entered POC study

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

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

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