EPAD
European Prevention of
Alzheimer's Dementia Consortium

The EPAD Approach: Using Longitudinal Data for Selection into Dementia Trials

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Background

- Consensus exists that the genesis of AD pathology predates dementia onset by over 20 years
- This presents an opportunity for disease course modification in the prodromal phase and even prior to appearance of clinical symptoms
- So, the accurate identification of high risk, non demented individuals to join secondary prevention trials is crucial

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EPAD= European Prevention of Alzheimer's Dementia Consortium

EPAD project seeks to:

- develop disease models for risk prediction at earlier phases of the disease process
- create a readiness cohort as a source for participant selection into trials; resource to be used for selection into trials

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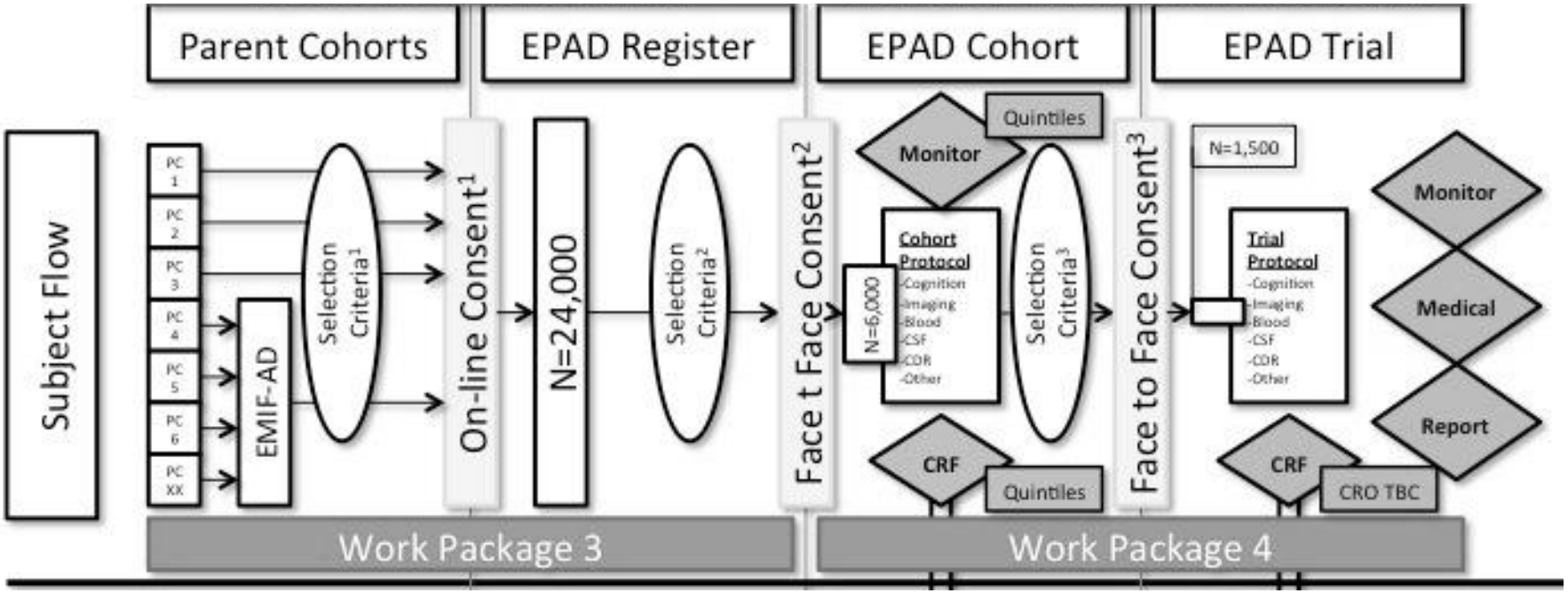
EPAD funnel



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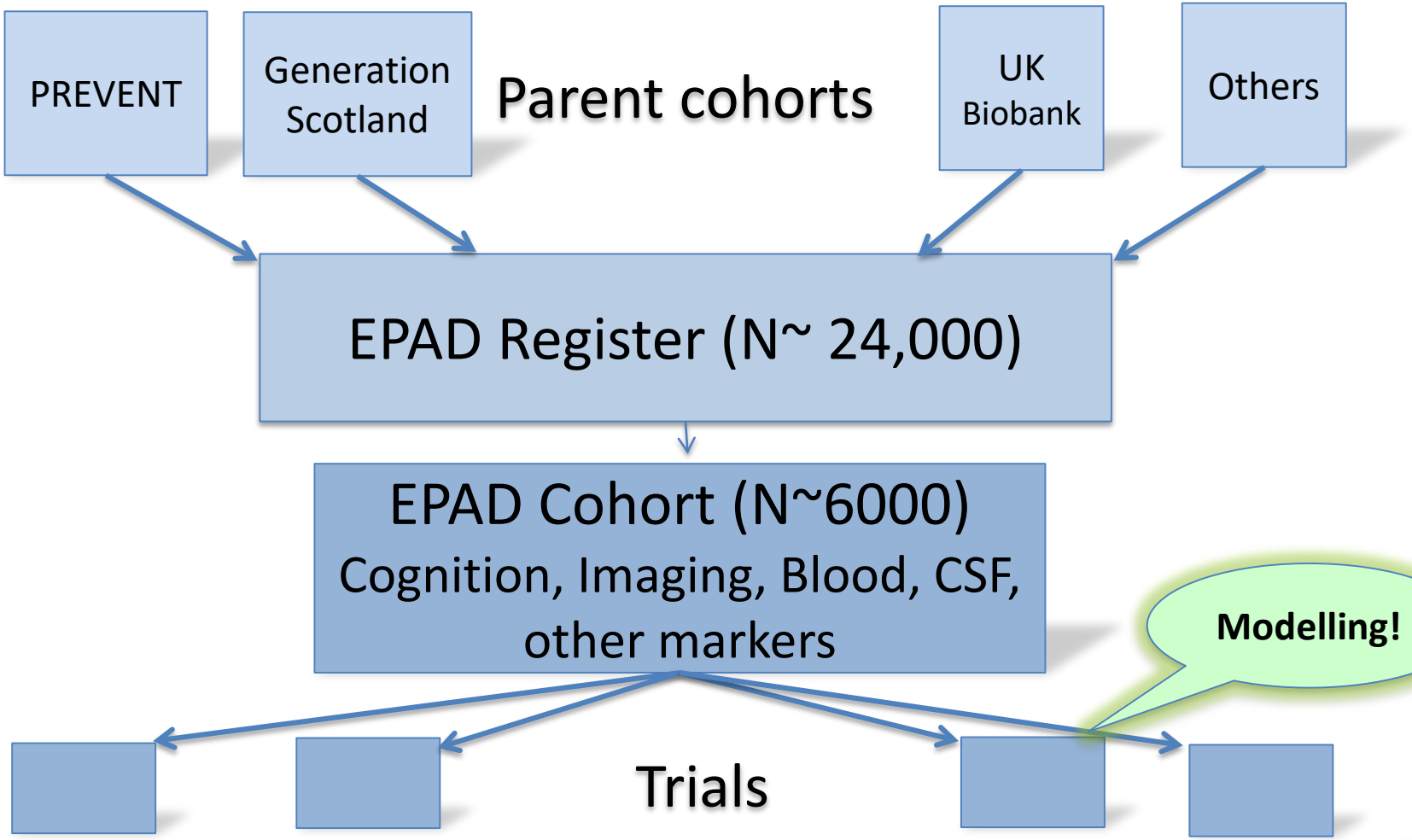
EPAD resource



EPAD LCS information

- Data from EPAD comprise:
  - cognitive outcomes RBANS total and domain specific scores
  - biomarkers CSF (e.g. amyloid beta, t-tau, p-tau), neuroimaging data (MRI) (e.g. hippocampal and whole brain volume, vascular burden)
  - risk factors (APOE, family history of AD/dementia), socio demographic factors (age, sex, education, etc)

Aim is to make best use of this rich information to identify individuals at higher risk of AD

How to identify these individuals?

- Existing dementia risk models recently reviewed and multiple limitations identified:
  - no internal validation, no model transportability, *usually developed in samples "closer" to disease manifestation*
  - methodologically limited (upcoming presentations)
  - most ignore information about change in markers, which is at the core of the process that we are aiming to predict

To sum: traditional methods may not be right tools for identification of higher risk individuals at an early stage for dementia

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"Disease modelling"

- we will consider a latent class model to identify groups of individuals whose trajectories over time are similar.
- we will define a latent variable that reflects information from multiple markers that are being tracked (cognitive scores, biomarkers, etc)
- these are assumed to be different noisy measurements of a single underlying AD process (unobserved)
- additional information (observed markers, risk factors) will also be considered within declining group

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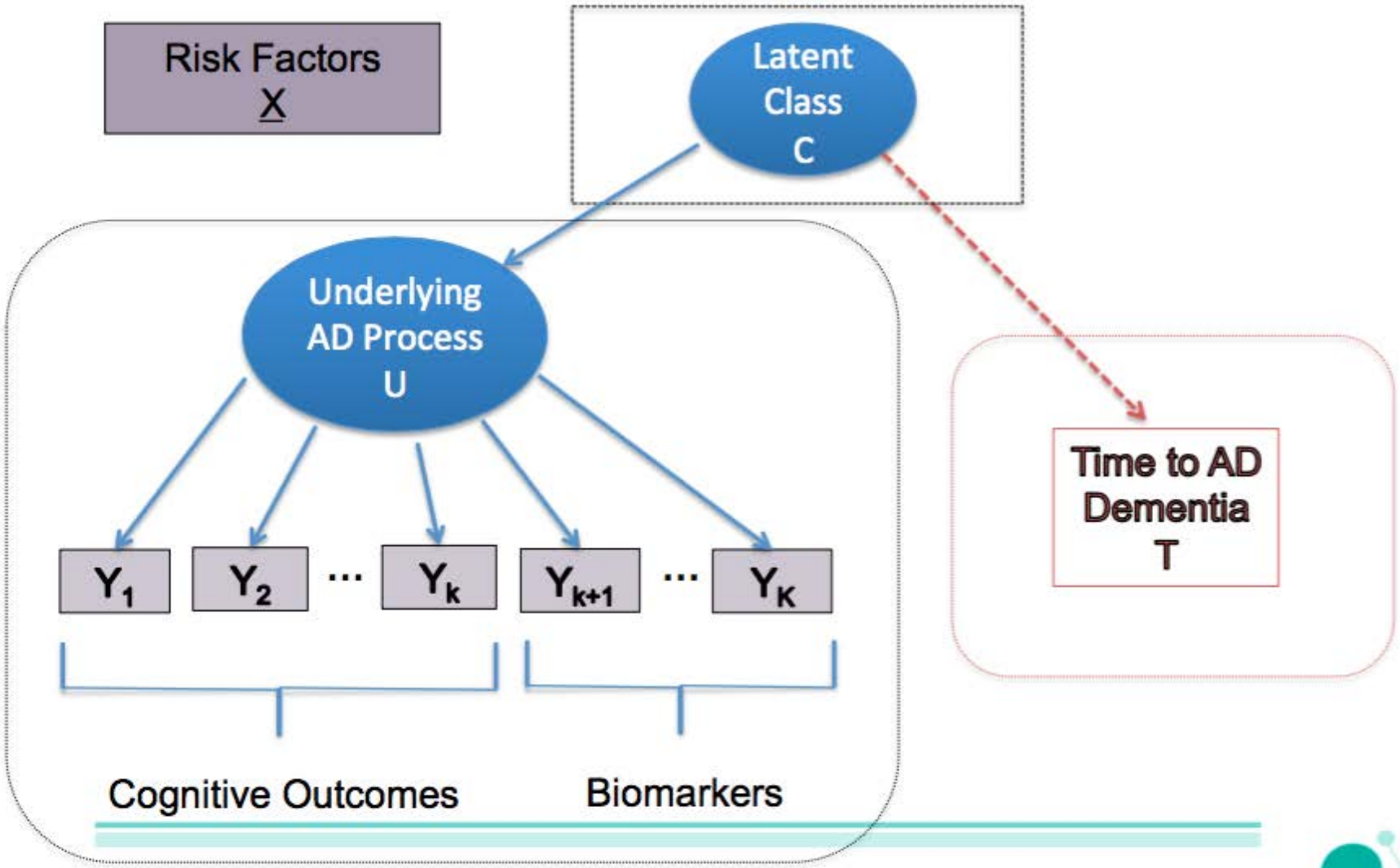
Conceptual Diagram



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Joint latent class model for multivariate outcomes & time-to-event

- Latent class membership model, $P(C_i=c| X_{0i})$
  - Multinomial logistic with covariates X_{0i}
- Structural model for underlying AD process, given class c

$$U_{ci}(t) = X_{1i}(t)^T \beta_c + Z_i(t)^T u_{ic}$$

- Outcome-specific observation model, given class c

$$h(Y_{kij};\eta_k) = U_{ci}(t_{kij}) + X_{2i}(t_{kij})^T \gamma_{kc} + b_{kci} + \varepsilon_{kij}$$

- Time-to-event model, given class c
  - Class-specific proportional hazards or parametric model with covariates $X_{3i}(t)$

Over time

- *individuals who are assigned by the model to the declining group will be selected to enter trials*
- models & risk scores will be continuously updated as new information is collected over time
- approach will not only identify “high risk” individuals, but will also allow to tease out what the contributors are for each individual
- participants being recruited to EPAD LCS. Limited influence of disease modelling in early stages of EPAD LCS (need data!), but will increase over time
- currently, we are in “testing mode” using existing data (ADNI), though only limited information available

Opportunities

- substantive work and results from variety of trials run using EPAD data will generate new knowledge about AD
- it is also a fantastic platform for sub studies
- dataset incredibly rich resource for methodological developments

- Contact me if interested.