Baseline ICV-adjusted Hippocampal Volume as a Biomarker for Enrichment in Alzheimer's Disease Trials

Co-Chairs: Patricia Cole (Takeda) & Derek Hill (IXICO)

A Modeling Approach to Demonstrate Trial Enrichment Beyond *Status Quo*

(Supported by the CAMD AD Modeling & Simulation Team)

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Critical Path Institute

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C-Path Data Mapping and Integration Process

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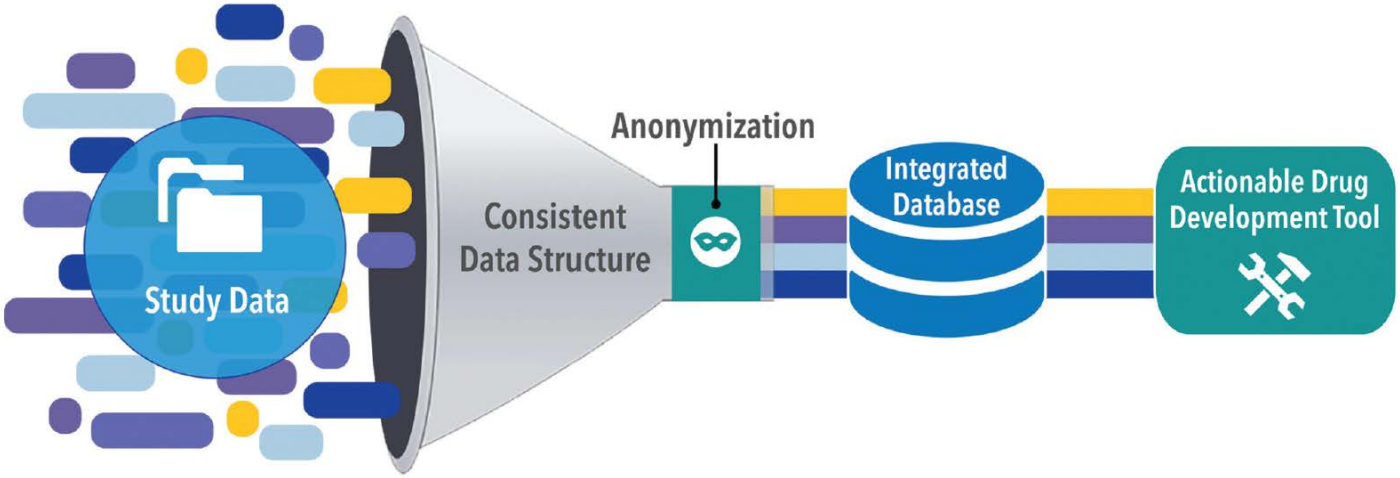
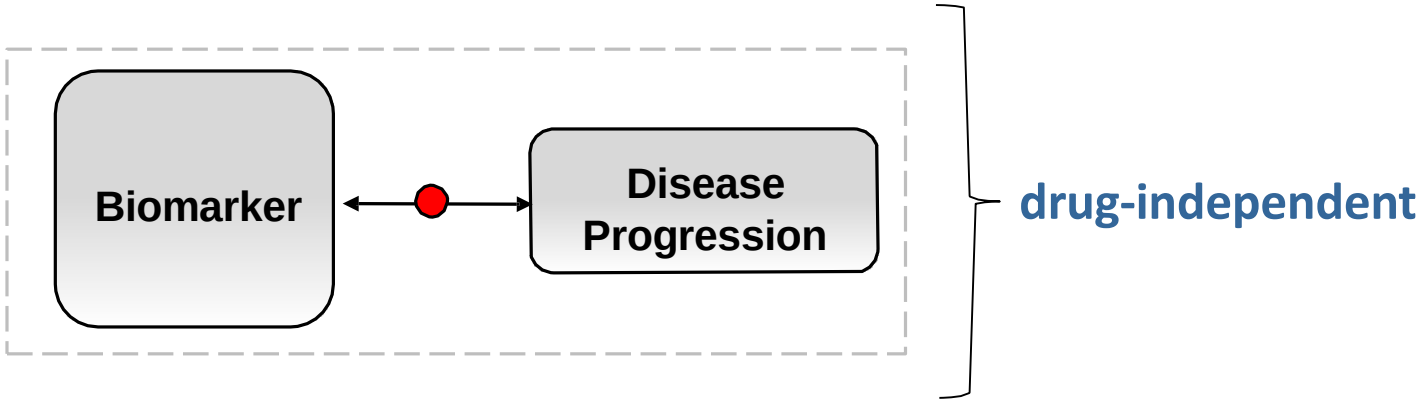
Application of Clinical Data Interchange Standards Consortium (CDISC) data standards



This illustrates the process of taking non-standardized data from individual studies, applying CDISC standards so all the data can be aggregated, and utilizing that fully integrated database to support the delivery of drug development tools.

DEVELOPMENT OF QUANTITATIVE TOOLS TO SUPPORT BIOMARKER QUALIFICATION

1. Fundamental component of biomarker-disease models
   - Biomarker-disease models are drug-independent
   - Can be used to optimize entry criteria



APPLICATION: TRIAL ENRICHMENT

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

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Clinical Medical

Trial Enrichment

- Improve the likelihood of clinical trial success by identifying a patient population that can discriminate between active and inactive drug treatment.
- Calculations may be performed to determine the sample size for
  - specific clinical cut-offs
  - patient characteristics
  - study duration
- Provide sufficient power to detect statistically and clinically relevant differences between a candidate drug vs. placebo

MODEL-BASED CLINICAL TRIAL ENRICHMENT PLATFORM: PROPOSED CONTEXT-OF-USE STATEMENT

- **General Area:** ICV-HV as a prognostic clinical trial enrichment biomarker for studies in amnestic MCI (aMCI) subjects
- **Target Population for Use:** Patients with aMCI. Clinical symptoms of aMCI are defined for this purpose as MMSE scores between 24-30 (inclusive), a memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia (ADNI criteria).
- **Stage of Drug Development for Use:** All clinical stages of drug development in aMCI, including proof of concept, dose-ranging, early efficacy and safety clinical studies through clinical trials for registration of a therapy in aMCI
- **Intended Application:** Clinical trial enrichment for aMCI Phase II and Phase III studies, based on the prognostic imaging biomarker ICV-HV as a predictor of disease progression
- **Out of scope:** Diagnostic, pharmacodynamic, efficacy marker of progression

MODEL STRUCTURE

Non-linear mixed-effects model

- **Independent variable**
  - Time
- **Dependent variable**
  - Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) scores
- **Covariates**
  - Sex *Status Quo*
  - Age at baseline
  - Disease severity at baseline (baseline CDR-SB)
  - ApoE genotype
  - Intracranial volume-adjusted hippocampal volume (ICV-HV) at baseline

SUPPORTING DATA

An integrated and standardized database of unique patient-level MCI data from the following sources:

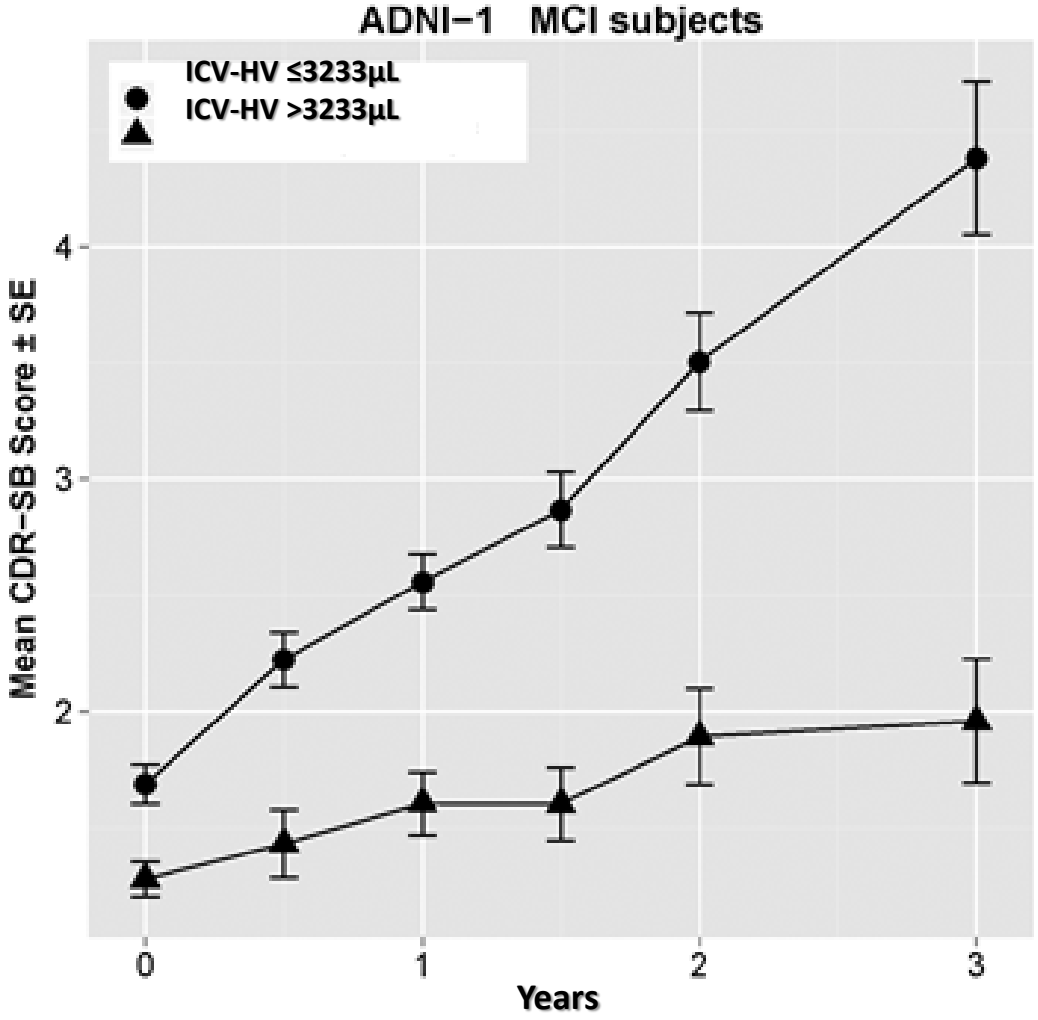
Study Name	Contributor	Type of Study	Number of MCI Subjects (Trial Total)
ADNI-1	ADNI	Observational	305 (400)
ADNI-2	ADNI	Observational	122 (163)
InDDEx (control arm)	Novartis	Clinical trial	394 (510)

MCI = mild cognitive impairment
ADNI = Alzheimer's Disease Neuroimaging Initiative
InDDEx = Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon™

PRELIMINARY FINDING IN ADNI-1

Preliminary model-based analyses in ADNI-1 show differential progression, according to baseline ICV-HV (Freesurfer™, 1SD below the mean ICV-HV of healthy controls).

Provided by Dr. Mahesh Samtani (J&J)



ENRICHMENT STRATEGY

Approximately 25% reduction with sample size

Provided by Dr. Kaori Ito (Pfizer)

MODEL ANALYSIS PLAN (MAP): KEY DELIVERABLES

- Along with a complete modeling and analysis report (**A**), the following deliverables are planned to aid with clinical trial enrichment and design:

  - (**B**) An R package for ICV-HV enrichment platform

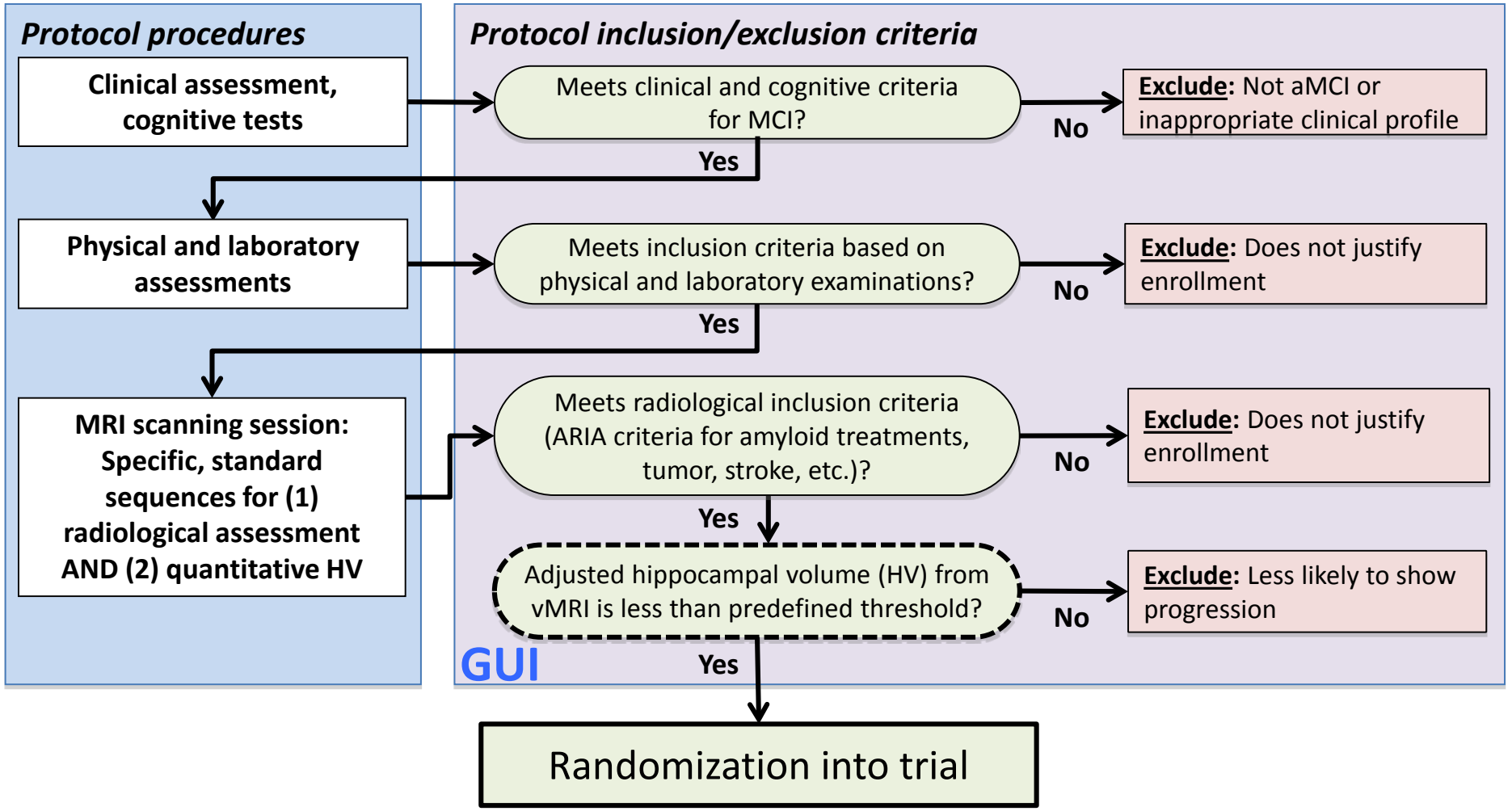
  - (**C**) A graphical and user-friendly web-based ICV-HV enrichment platform

- These tools will inform user-defined individual characteristics at study entry including cut-offs of ICV-HV for enrichment

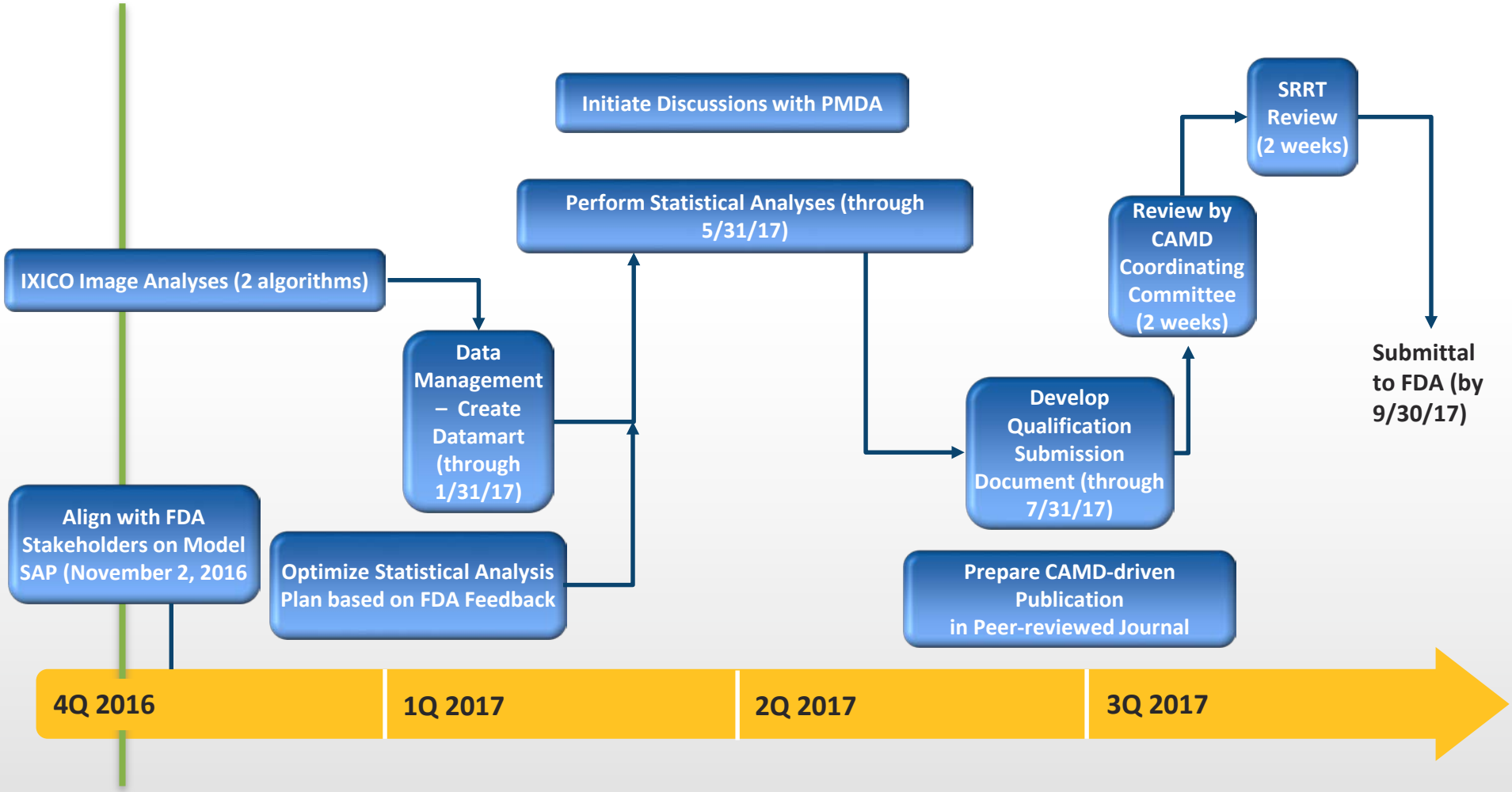
PROPOSED IMPLEMENTATION

1. Sponsor will identify the expected therapeutic effect of the drug candidate based on internal knowledge
2. Sponsor will define a set of individual characteristics at study entry accounting for relevant covariates (e.g., baseline CDR-SB, baseline age, sex, *ApoE* genotype, ICV-HV)
3. Sponsor will use the model, inputting **1** and **2**, to run clinical trial simulations and determine trial characteristics (e.g., sample size, trial duration) that will be able to detect the expected therapeutic effect with sufficient power (e.g., 80%)
4. Based on results obtained in **3**, sponsor may decide to change entry characteristics (**2**), and re-run clinical trial simulations (**3**) until trial characteristics are optimal (**iterative process**)

EXAMPLE DECISION TREE FOR TRIAL ENRICHMENT USING HV COMPUTED FROM VMRI



HIPPOCAMPAL VOLUME IMAGING BIOMARKER TEAM – TIMELINE



AD HIPPOCAMPAL VOLUME IMAGING TEAM

- **ADM Diagnostics** – Dawn Matthews
- **Alzheimer's Association** – Maria Carrillo and James Hendrix
- **Bioclinica** – Joel Schaerer, Joyce Suhy, and Luc Bracoud
- **Boehringer Ingelheim** – Mark Gordon
- **Critical Path Institute** – Steve Arneric, Volker Kern, Klaus Romero, Daniela Conrado, and Jenn Ferstl
- **Eli Lilly** – Adam Schwarz
- **IXICO** – Derek Hill, Katherine Gray, and Robin Wolz
- **Janssen R&D** – Jerry Novak
- **Novartis** – Richard Meibach and Paul Maguire
- **Pfizer** – Kaori Ito and Sean Xie
- **Takeda** – Patricia Cole
- **Roche Genentech** – Tracie Carey
- **UC Davis** – Laurel Beckett

Note: Team Co-Chairs are underlined

Thank you

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