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CAMD

Coalition Against Major Diseases

*Marc Cantillon MD
Executive Director*

Founded by



CRITICAL PATH
INSTITUTE

Improving the Path for Innovative Therapies

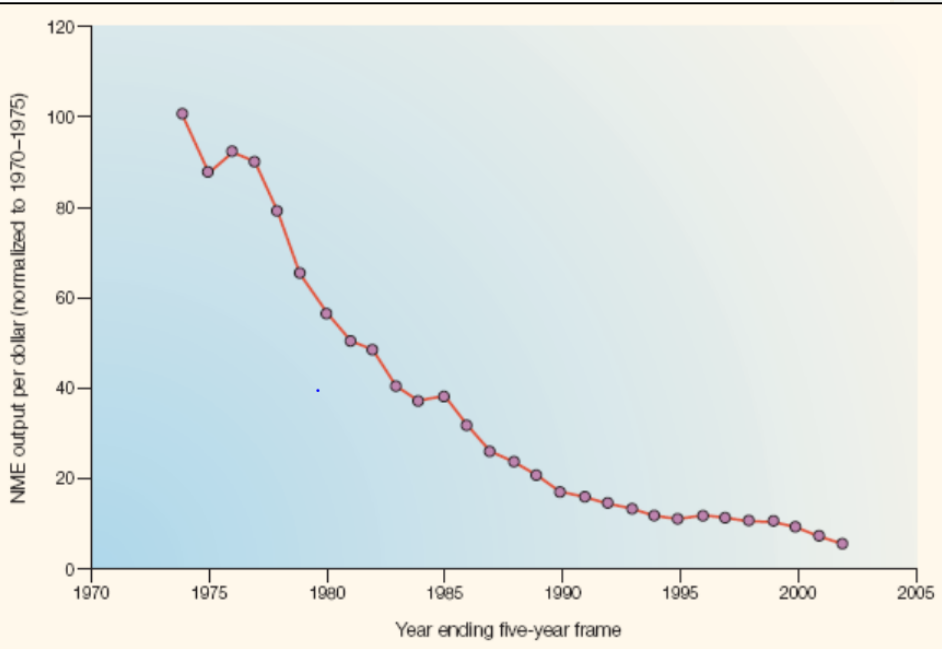
In collaboration with



ENGELBERG CENTER for
Health Care Reform
at BROOKINGS

FDA's 2004 Message: Find the "Critical Path"

Productivity
Death Spiral



Coalition Against Major Diseases



CAMD

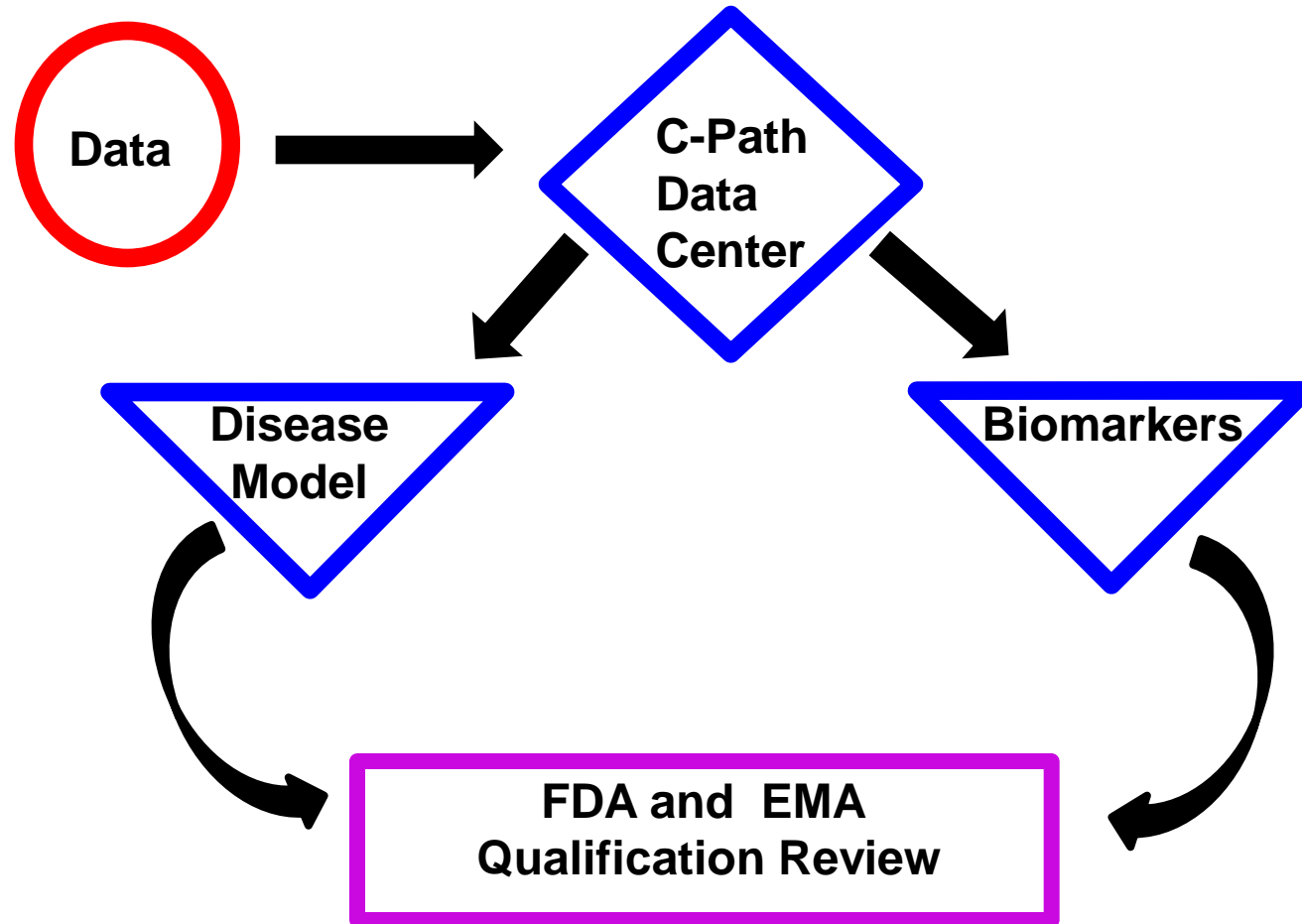
Patients

Government

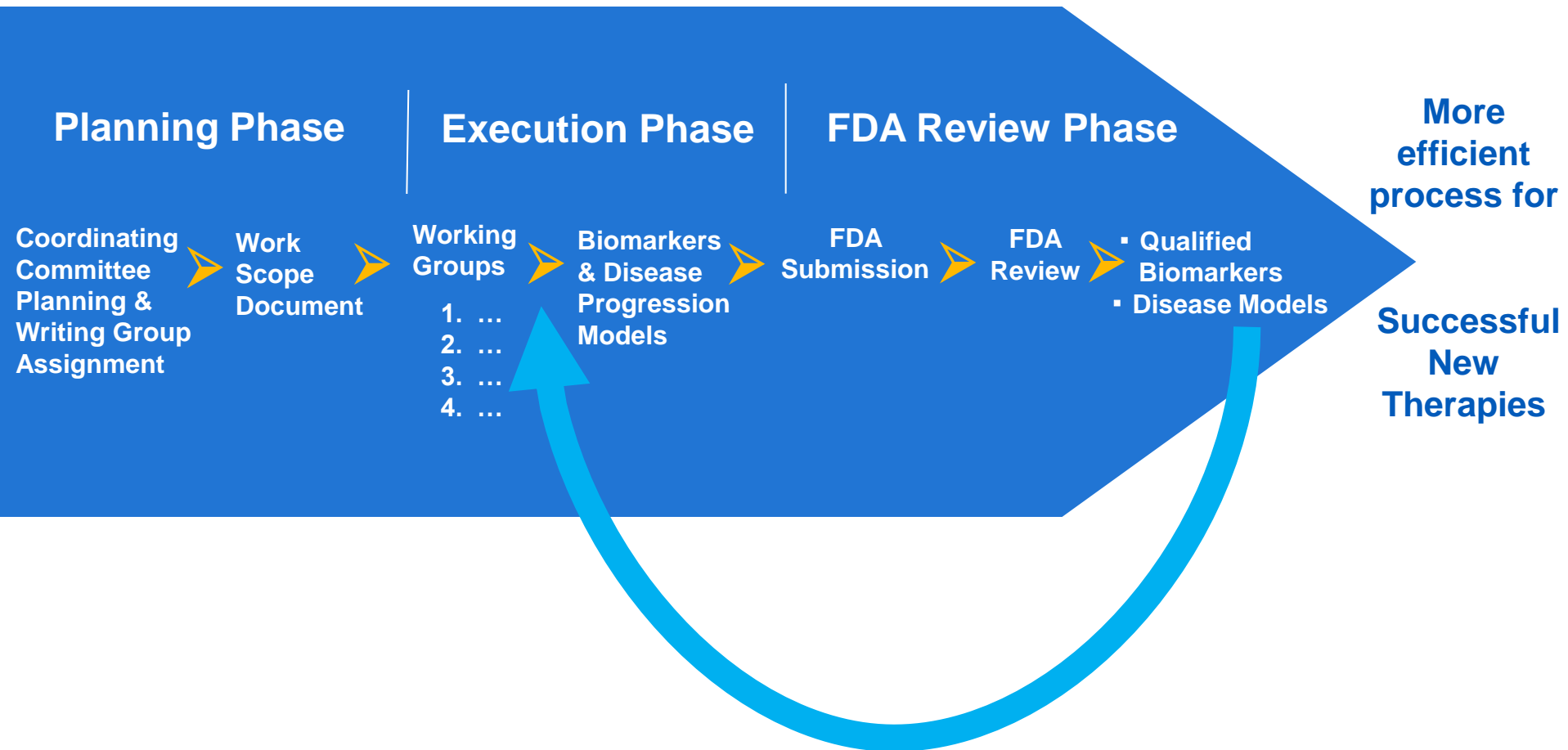
Industry



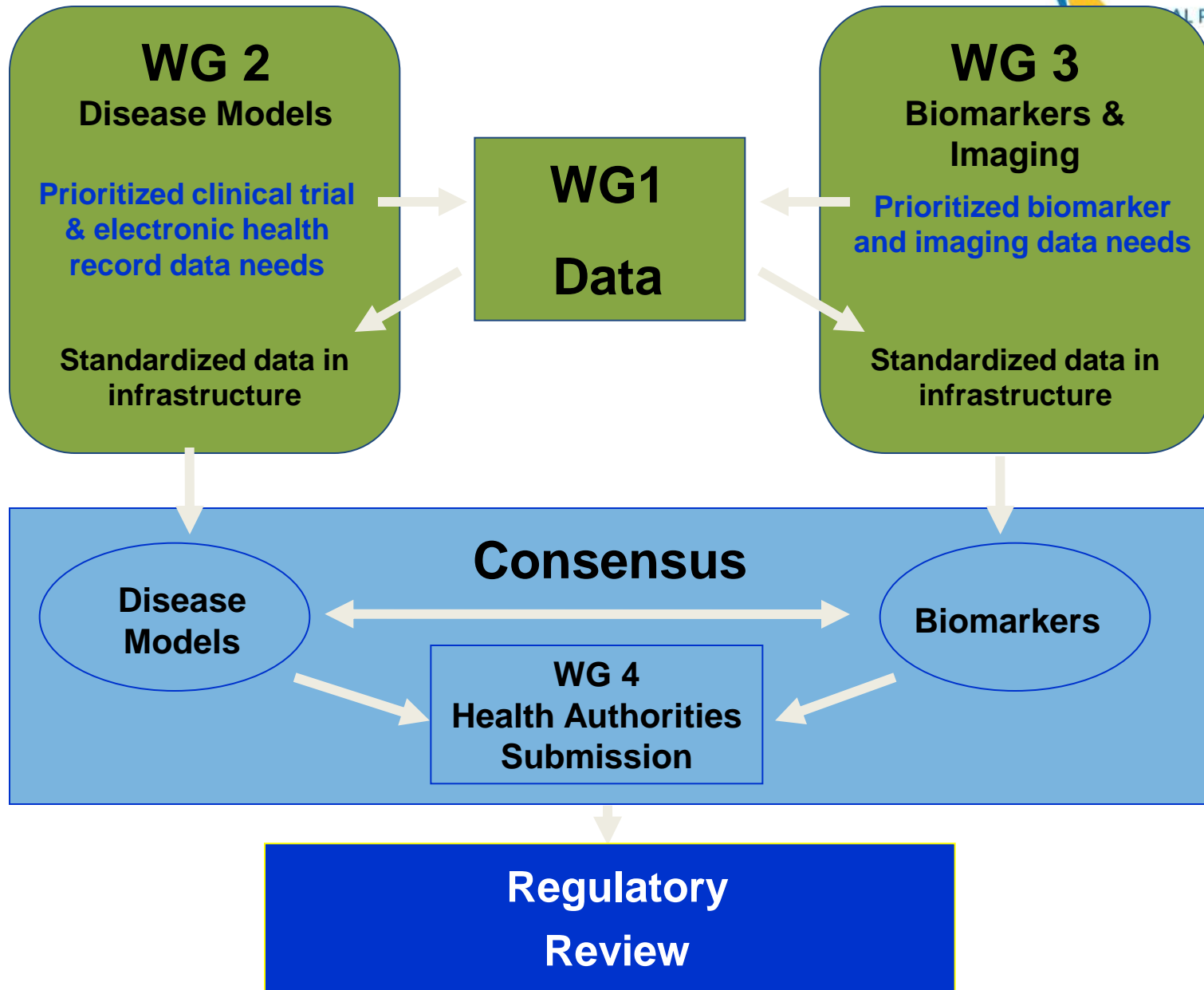
Process



Roadmap



Workgroup Workflow

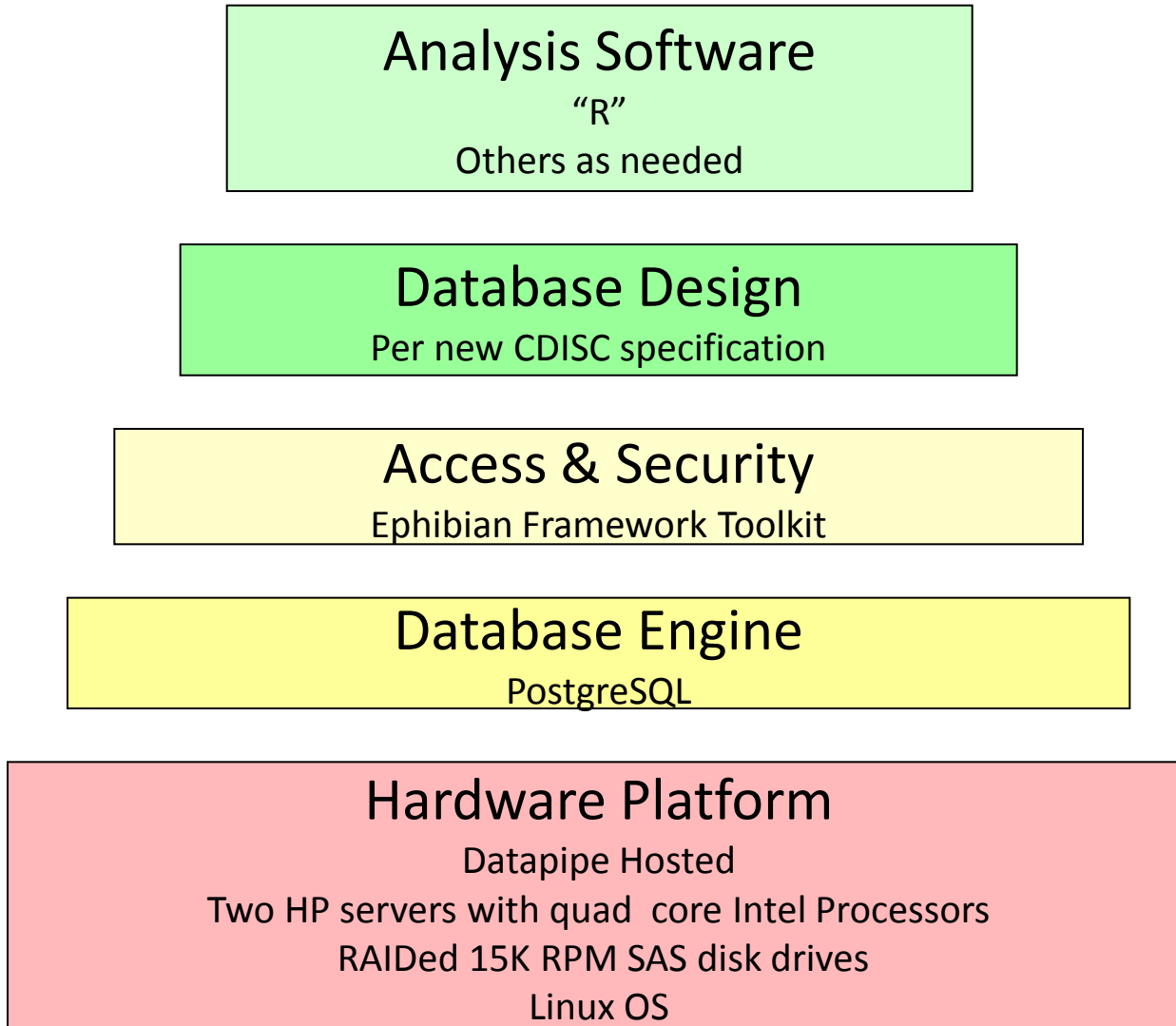


Data Workgroup



- Mission : support Biomarker and model workgroups with data
- Produced a battery of Alzheimer's data standards in CDISC (Clinical Data Interchange Standards Consortium)format
- Annotated case report forms for clinical scales based on agreed approaches to data capture
- Defined terminology for populating results in SDTM (Study Data Tabulation Model, recommended FDA 2004)
- Accumulating industry AD and MCI placebo controlled data in CDISC format to form large pool of accessible data
- Expect full access by qualified researchers

Database Infrastructure



The Data Requirements



- Completed phase II-IV AD and PD trials
- Duration > 6 months
- Placebo arm data
- Supporting Documentation Required
 - CDISC Annotated CRFs
 - Protocol (or excerpts thereof)

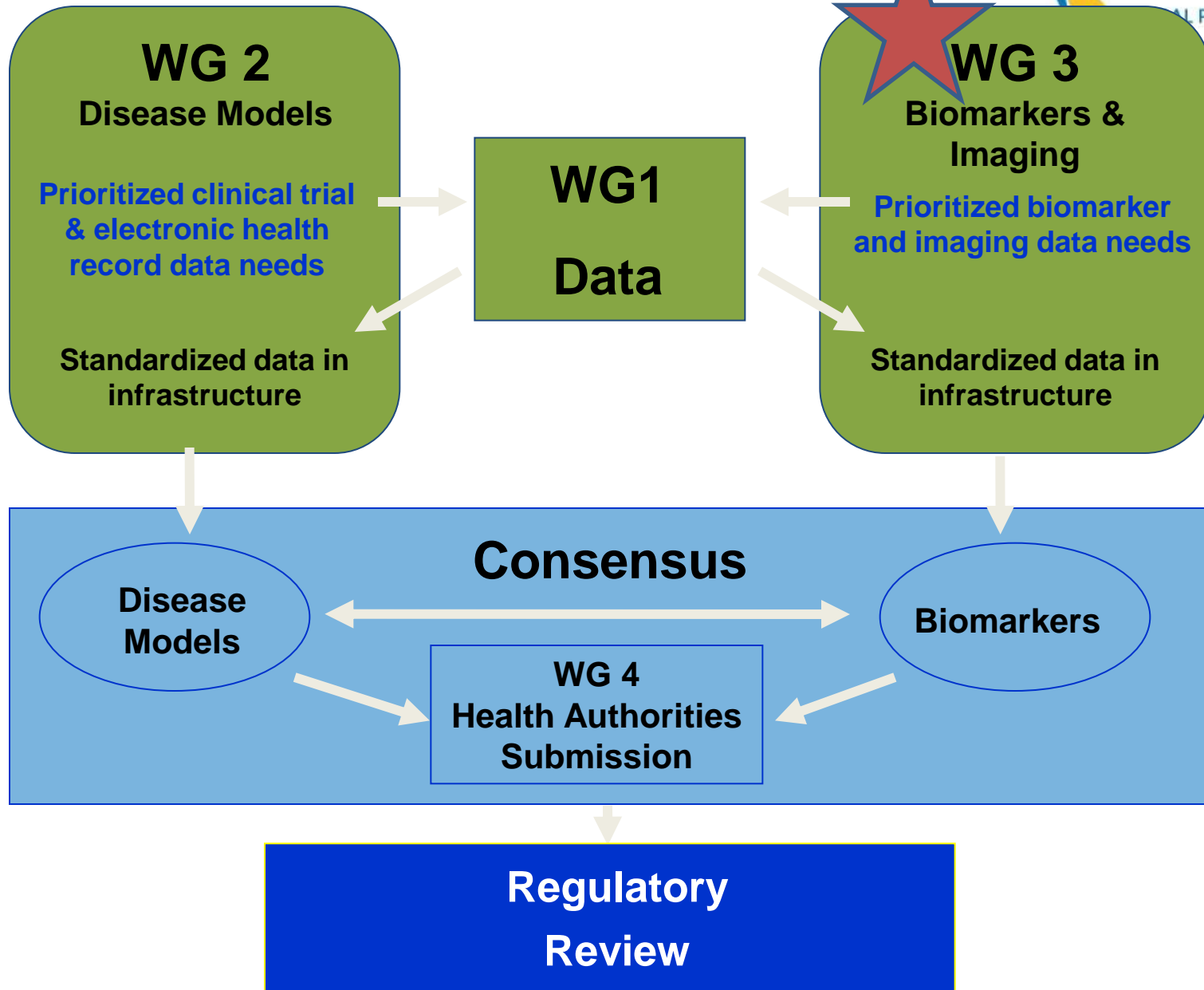
PUBLIC RELEASE OF ALZHEIMER'S CLINICAL TRIAL DATA BY PHARMACEUTICAL RESEARCHERS

**First Combined Pharmaceutical Trial Data on Neuro-degenerative Diseases;
Shared Resource from Unique Public-Private Partnership Will Help
Accelerate Alzheimer's, Parkinson's, and Other Brain Disease Research**

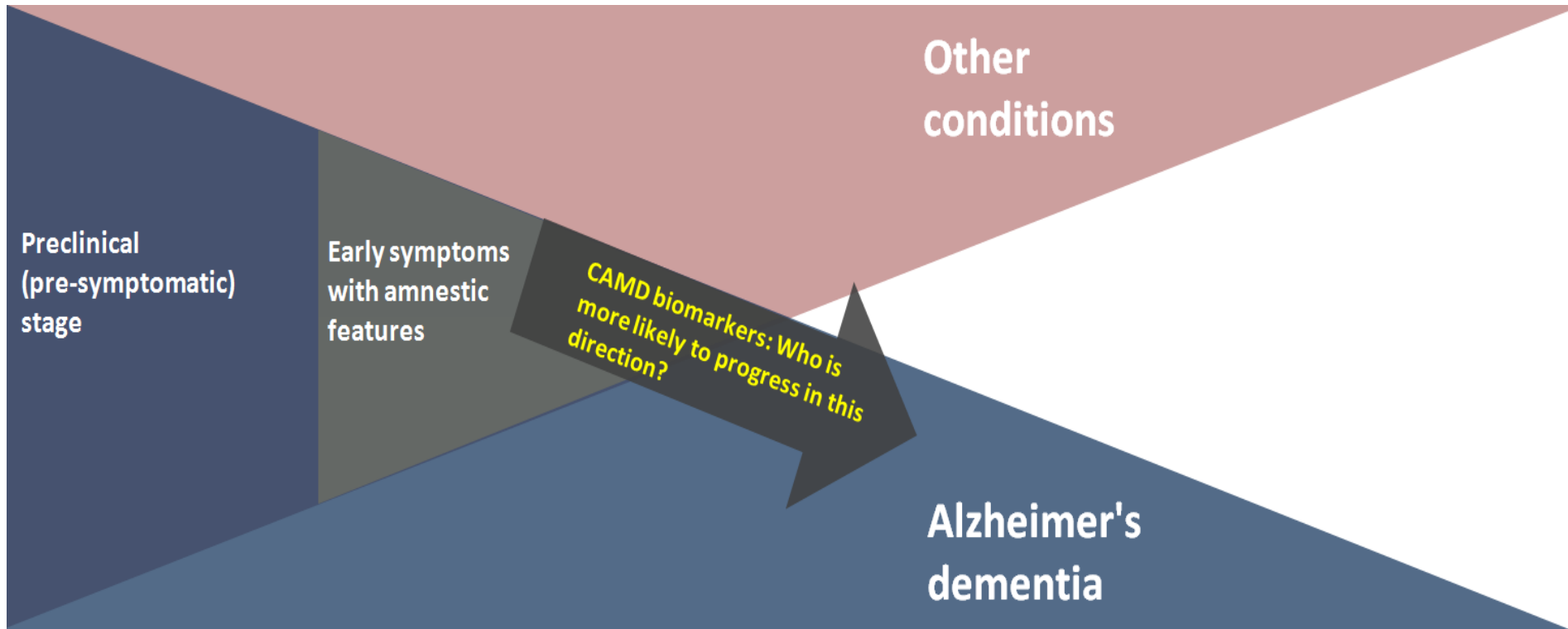
Washington, DC – A new database of more than 4,000 Alzheimer's disease patients who have participated in 11 industry-sponsored clinical trials will be released today by the Coalition Against Major Diseases (CAMD).

This is the first database of combined clinical trials to be openly shared by pharmaceutical companies and made available to qualified researchers around the world.

Workgroup Workflow



Biomarkers



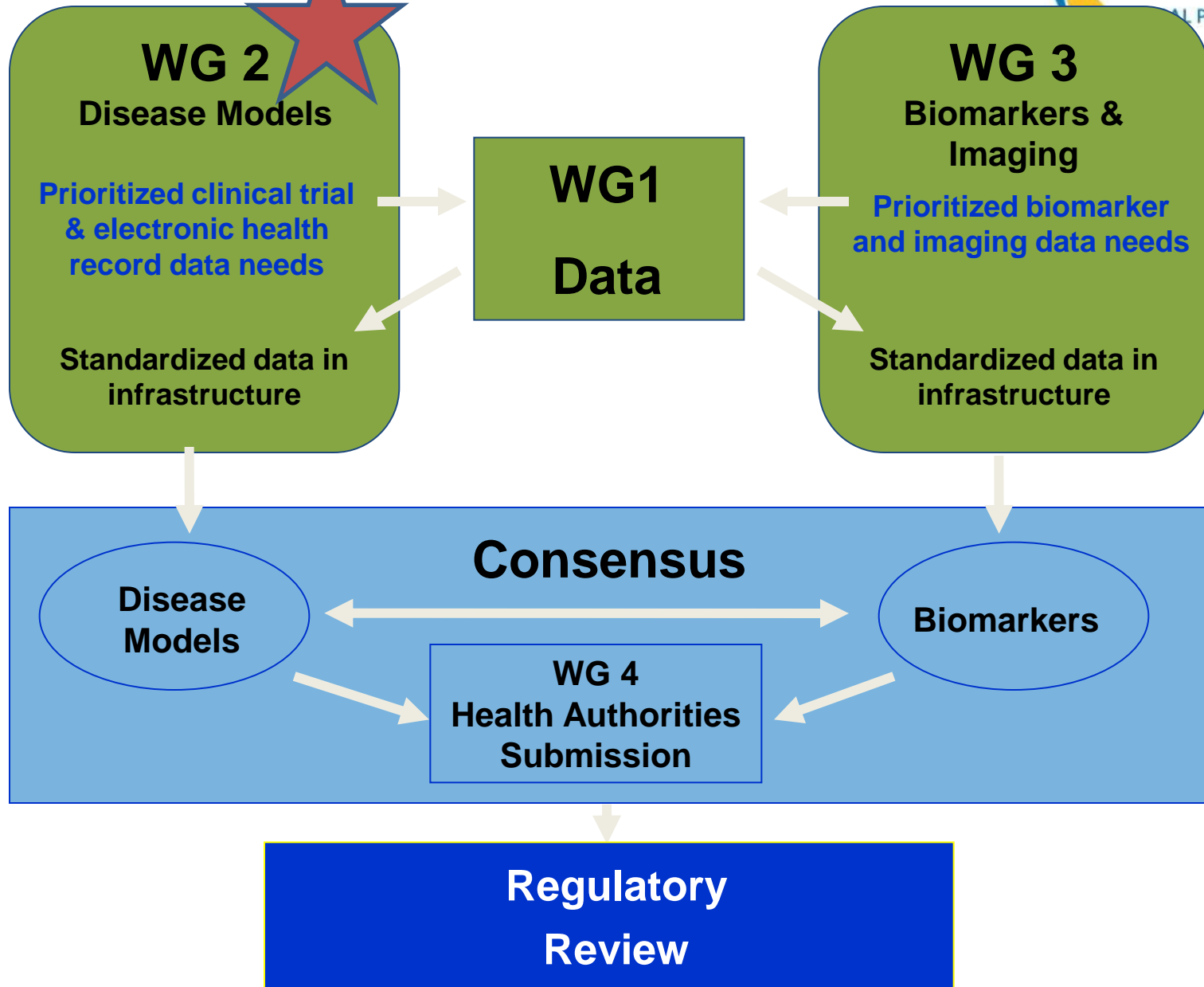
AD: Advantages of approach



- Enables identification and intervention prior to the onset of dementia
- Increase likelihood of intervention success
- Progression to AD dementia within a reasonable time for trial may be study endpoint
- May shorten timelines or decrease study population numbers
- More uniform patient populations

The challenge is we are really asking the agency to qualify several biomarkers at once, an unparalleled attempt

Workgroup Workflow



Preliminary AD Model Concepts



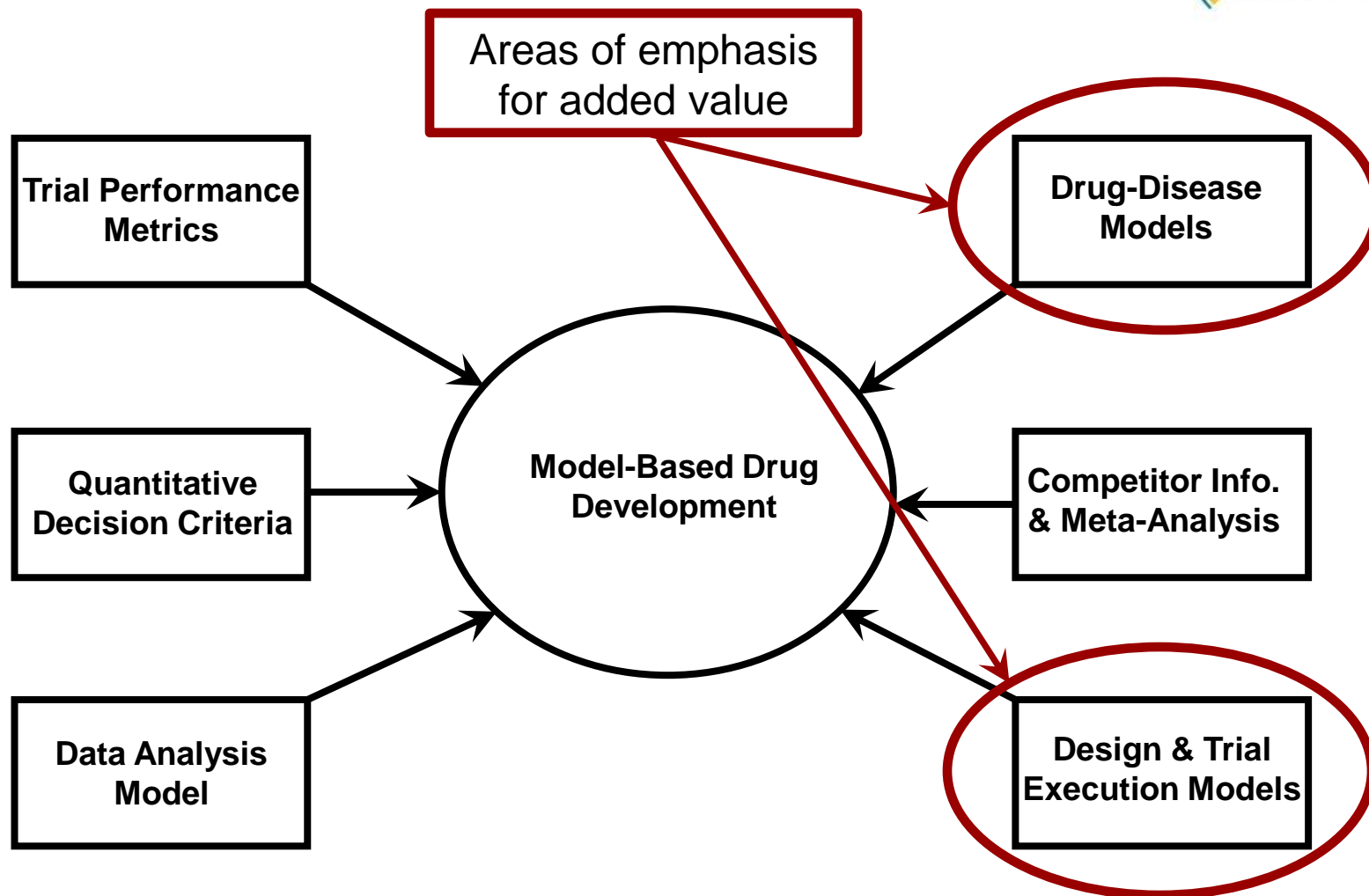
- Basic question:
 - What is the expected progression of Alzheimer's disease over time, as described by change in ADAS-cog scores?
- Basic principles:
 - Independent variable: time
 - Dependent variable: Δ ADAS-cog
 - Covariates: baseline cognitive test scores, demographics, biomarkers where available, etc.

Data for Model Development



- Literature (published)
 - Data represents 19,972 patients/84,441 observations
 - Useful for estimating interstudy variability and effect size of symptomatic agents
 - Limited to study means at various time-points
- ADNI (in press)
 - Normal/MCI/Mild AD in a natural history design
 - Rich imaging and biomarker dataset
- Sponsor Trial database

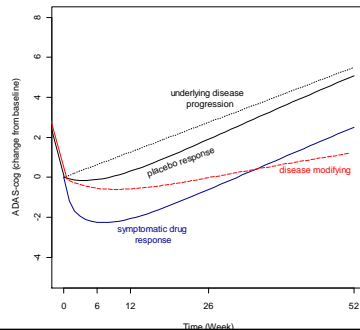
Components of Model-Based Drug Development



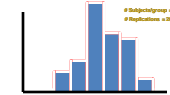
Evaluate “what if” scenarios.....

Run Multiple
Replications of Trial

Drug/Disease Model



Range of Outcomes



Trial Designs

- Doses/arms/N
- Duration/Sampling
- Freq and time
- Enrichment strategies

Data Analytics

Effect of Dose and Number of Subjects on Power to Estimate Significant Effect of Drug vs Placebo

N	1 mg	2 mg	5 mg	10 mg	20 mg
30	4.5	6.5	18	48.5	73.5
40	13	29	76	87	91
50	27.5	52	85	95	99
60	40.5	62	90	97	100
70	55.5	71	94	99	100

Modify Design

Progression Model Concepts

Basic concept:

$$S(t) = S_0 + \alpha \cdot t + \varepsilon$$

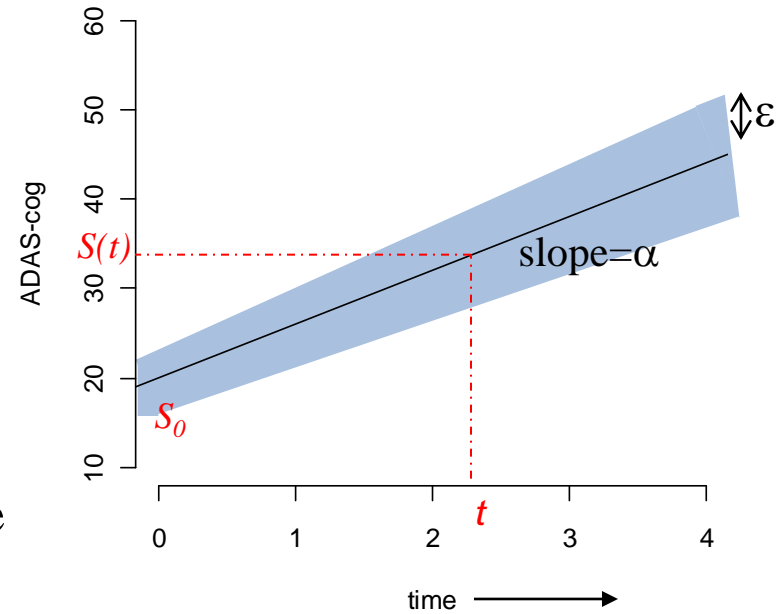
S_0 : baseline disease state

$S(t)$: expected state at a given point in time

α : disease progression rate

t : time

ε : prediction variability



AD Trial Model Components

$$S(t) = S_0 + \alpha \cdot t + f_{pbo}(t) + f_{drug}(t) + \varepsilon$$

S_0 : baseline disease “state”

$S(t)$: expected “state” at a time “t”

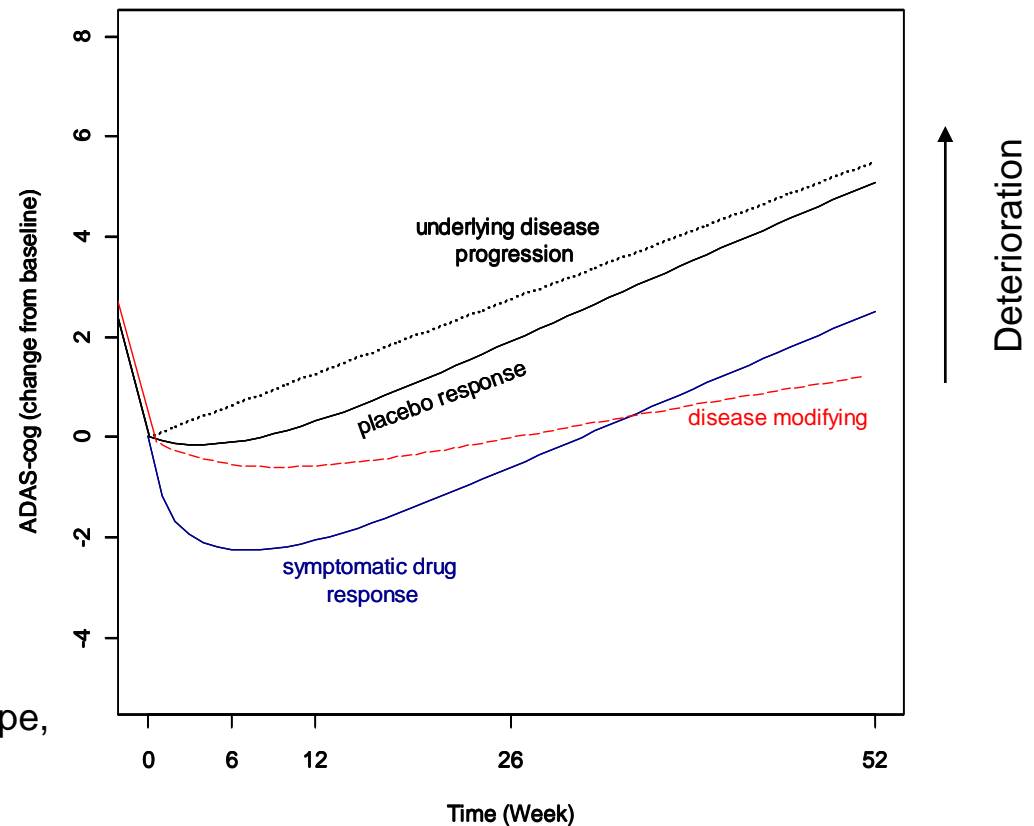
α : disease progression rate

t : time

ε : prediction variability

$f_{pbo}(t)$: placebo effect

$f_{drug}(t)$: symptomatic drug effects



Note: if the drug is disease modifying (DM) type, the effect is on the slope (α):

$$S(t) = S_0 + \alpha \cdot \underline{f_{DM}(t)} \cdot t + f_{pbo}(t) + \varepsilon$$

..or combination with symptomatic effect

Trial design factors to Consider

- Which (or how many) doses are most informative
- Sample size
- Trial duration
- Sensitivity for effects
- Impact of patient inclusion criteria
- Effect of attrition on analyses
- Comparison of designs' efficiency (development stages)
- Data analytic techniques

Framework for Research Plan



- Simulate clinical trial datasets based on:
 - The established model
 - The hypothesized drug effects
 - The candidate trial designs, using a range of feasible sample sizes, lengths, analysis types, etc.
- Compare operating characteristics based on the variation in results across simulated trial datasets

Relevance for Rare Diseases Development Path

In the future more initiatives will have to address the need for networking scientific knowledge and research capabilities to address the difficulties in generating data for rare diseases. Only collaboration can overcome the problems that the rarity of the diseases and the dispersion of patients put on the development of medicines for rare diseases.