ACCELERATING DRUG DEVELOPMENT FOR RARE DISEASES: ESTABLISHING A CORNERSTONE THROUGH DATA SHARING

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RARE DISEASE CURES ACCELERATOR
DATA AND ANALYTICS PLATFORM
LAUNCH MEETING

17th September 2019

Disclaimer: Dr. Budd Haeberlein is an employee of Biogen. The information in this presentation is based on the presenters' expertise and experience, and represents the views of the presenter.

PROBLEM

- There is a pressing need for a better-informed basis on which to design clinical trials
- The need to quantitatively characterize diseases is particularly acute in rare disease drug development as the information upon which to do so is limited

WHAT ARE THE CHALLENGES IN RARE DISEASE DRUG DEVELOPMENT?

SMALL HETEROGENEOUS POPULATIONS

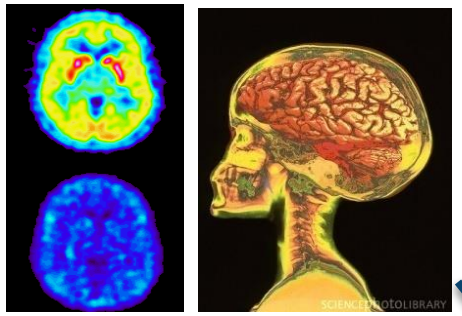
- Lack of disease characterization / disease progression
- High heterogeneity leading to variability in disease presentation & course
- Lack of comprehensive scientific understanding / mechanisms in disease
- Challenges of clinical trial designs
- Limited patient number & Geographic dispersal
- Underinformed outcome assessments and endpoints
- Underinformed or absent biomarkers
- Evolving standard of care

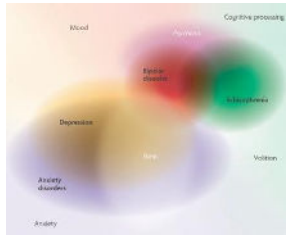
CAN RARE DISEASE DEVELOPMENT BENEFIT FROM LESSONS FROM LARGER DEVELOPMENT PROGRAMS?

- **These challenges are not unique to rare diseases, but are amplified in difficulty**
- **Smaller samples and paucity of data are also a challenge in early phases of drug development where critical go/no-go decisions are often based on:**
  - Limited data, smaller numbers of patients, information gaps, evolving disease understanding, need for informed decisions for Phase 3 design
  - All in setting of limited information, information is often limited to what you have available internally

CNS DISORDERS PRESENT CHALLENGES FOR DRUG DEVELOPMENT…

Potential Challenges
Uncertain target engagement ▪ Difficult to detect pharmacodynamic effects in CNS compartment
Population heterogeneity ▪ Syndromic classification
"Noisy readouts" ▪ Cognitive function, mood, psychosis, pain
Insidious onset and slow progression





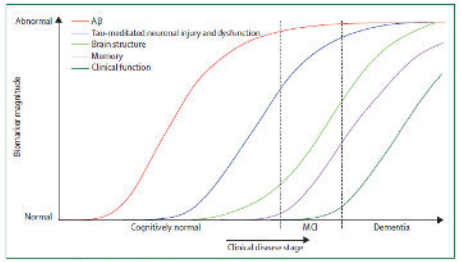


Figure 2: Dynamic biomarkers of the Alzheimer's pathological cascade
Aβ is identified by CSF-$Aβ_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

Potential Pitfalls
Errors in dose selection
Diagnostic uncertainty, imprecise staging of disease, Low responder rates
Need large numbers to detect treatment effect, ↓Data Quality
Larger and longer trials, ↓Data Quality, ↑ Missing data

↑ Variability of data

↓ Ability to detect treatment effect

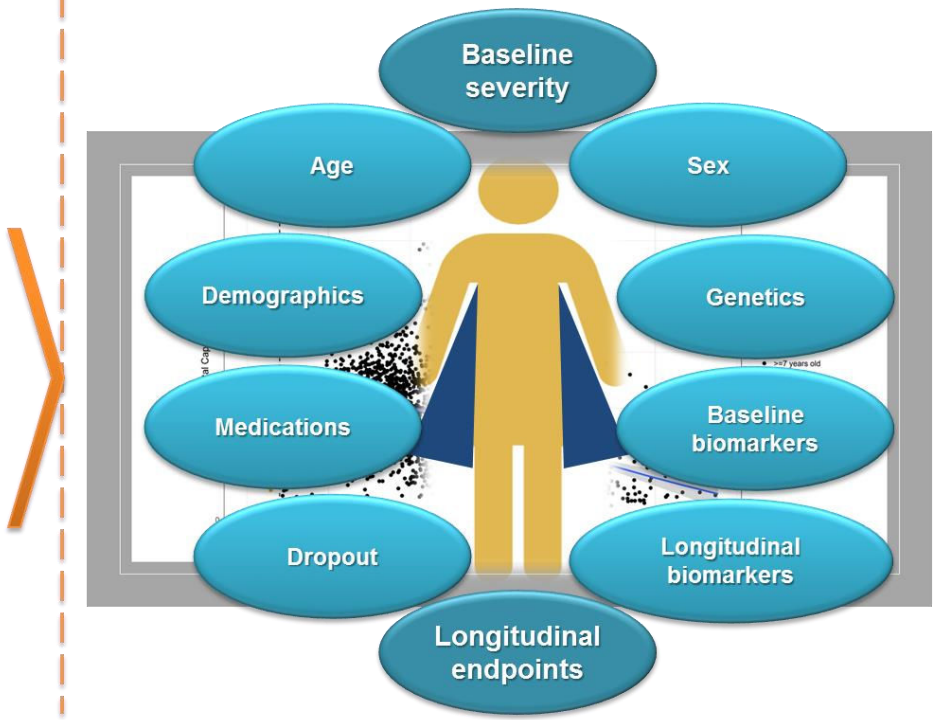
DATA SHARING PROVIDES THE KEY

- Data sharing, integration and quantification can de-risk decision-making by reducing uncertainty, across the drug development value chain (from translational, through early phase clinical development, to registration studies)

Input

Patient-level data

Modeling



Output

Characterization of disease

Baseline

Trajectory

Rate

Predictors

Web Clinical Trial Simulator

IMPACTFUL GLOBAL DATA ACCESS FOR INDUSTRY AND RESEARCHERS: ALZHEIMER'S CASE STUDY

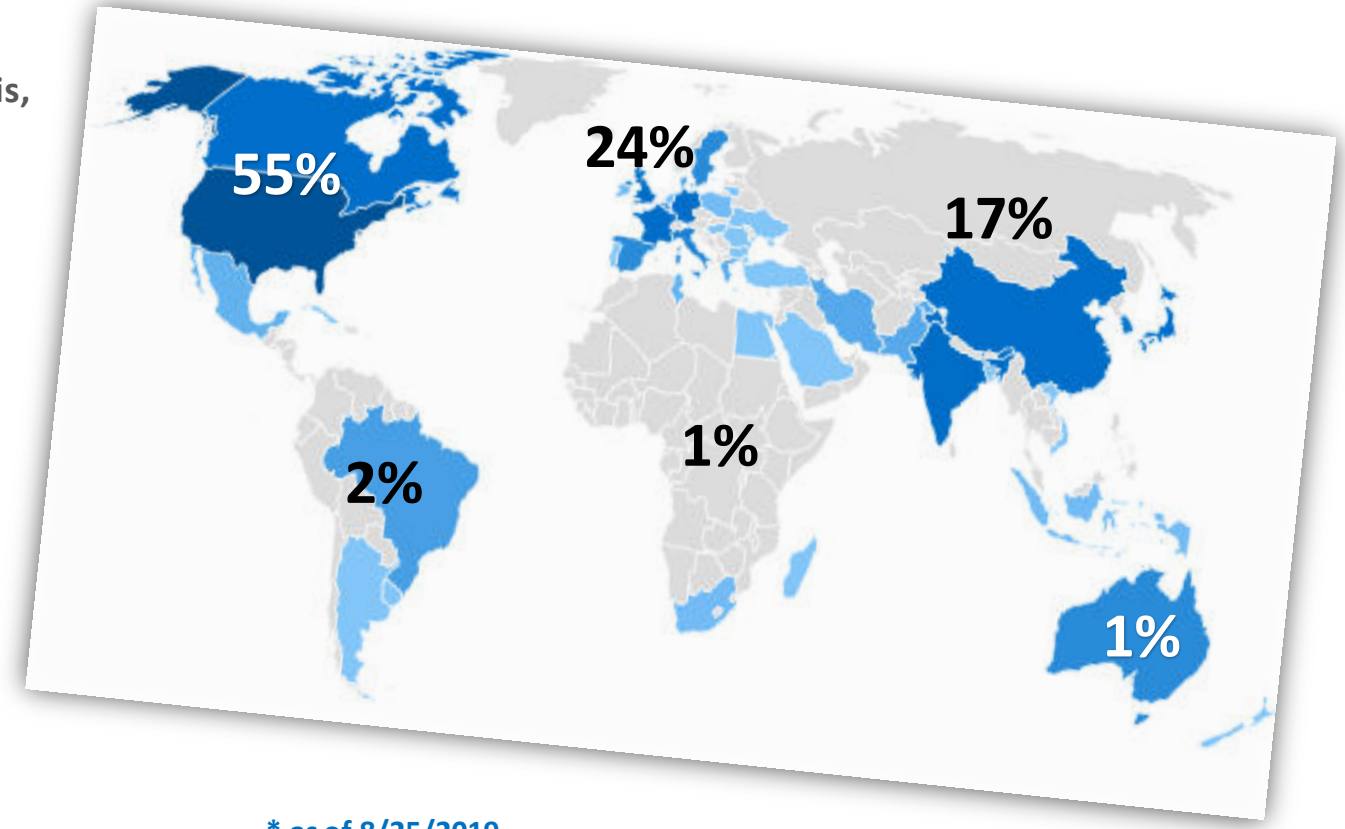
CRITICAL PATH INSTITUTE

38 AD studies with 14,583 individual anonymized patient records and more than 420,000 covariate measurements

(shared by Abbott Laboratories, AstraZeneca, Bellus Health, Eisai, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer, Sanofi, Servier, and ADCS)

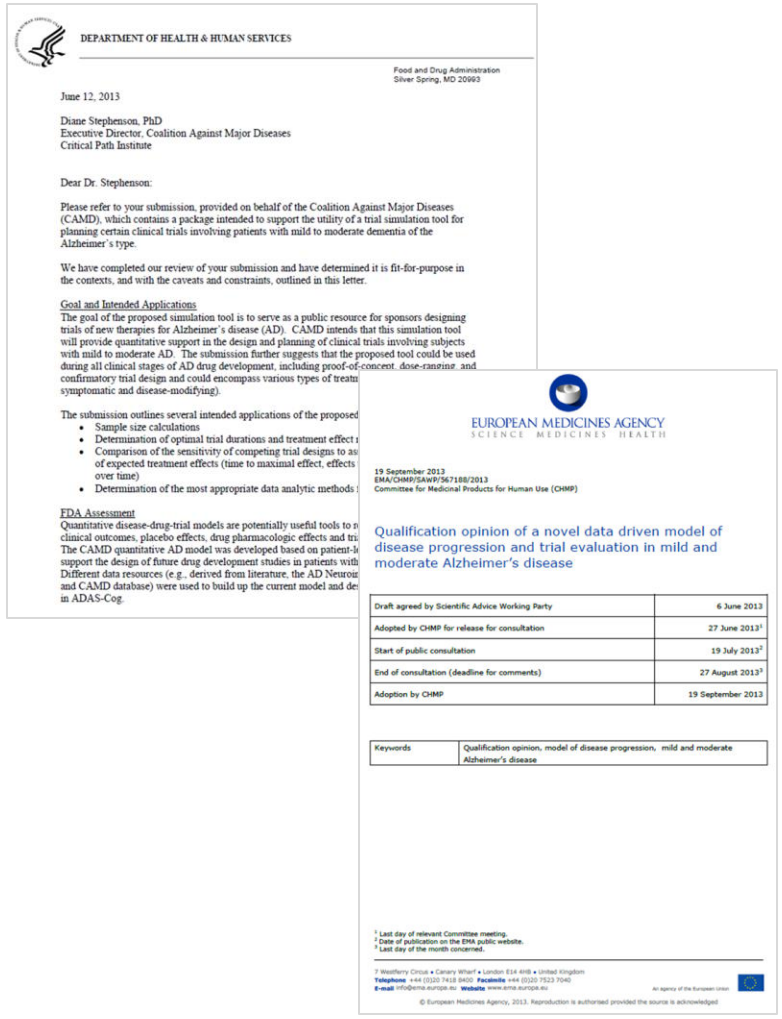
486* approved applicants from 385+ distinct institutions from 52 countries

- Pharmaceutical Industry
- Government Agencies
- Non-profit Organizations
- Academia
- Independent Researchers



* as of 8/25/2019

ALZHEIMER'S DISEASE CLINICAL TRIAL SIMULATOR: REGULATORY-ENDORSED TOOL MADE POSSIBLE BY DATA SHARING, COLLABORATION AND QUANTITATION



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

June 12, 2013

Diane Stephenson, PhD
Executive Director, Coalition Against Major Diseases
Critical Path Institute

Dear Dr. Stephenson:

Please refer to your submission, provided on behalf of the Coalition Against Major Diseases (CAMD), which contains a package intended to support the utility of a trial simulation tool for planning certain clinical trials involving patients with mild to moderate dementia of the Alzheimer's type.

We have completed our review of your submission and have determined it is fit-for-purpose in the contexts, and with the caveats and constraints, outlined in this letter.

Goal and Intended Applications

The goal of the proposed simulation tool is to serve as a public resource for sponsors designing trials of new therapies for Alzheimer's disease (AD). CAMD intends that this simulation tool will provide quantitative support in the design and planning of clinical trials involving subjects with mild to moderate AD. The submission further suggests that the proposed tool could be used during all clinical stages of AD drug development, including proof-of-concept, dose-ranging, and confirmatory trial design and could encompass various types of treatm
symptomatic and disease-modifying).

The submission outlines several intended applications of the proposed
- Sample size calculations
- Determination of optimal trial durations and treatment effect
- Comparison of the sensitivity of competing trial designs to as
of expected treatment effects (time to maximal effect, effects
over time)
- Determination of the most appropriate data analytic methods

FDA Assessment

Quantitative disease-drug-trial models are potentially useful tools to
clinical outcomes, placebo effects, drug pharmacologic effects and tri
The CAMD quantitative AD model was developed based on patient-l
support the design of future drug development studies in patients with
Different data resources (e.g., derived from literature, the AD Neurol
and CAMD database) were used to build up the current model and de
in ADAS-Cog.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2013
EMA/CHMP/SAWP/567188/2013
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease

Draft agreed by Scientific Advice Working Party	6 June 2013
Adopted by CHMP for release for consultation	27 June 2013[1]
Start of public consultation	19 July 2013[2]
End of consultation (deadline for comments)	27 August 2013[3]
Adoption by CHMP	19 September 2013

Keywords	Qualification opinion, model of disease progression, mild and moderate Alzheimer's disease

[1] Last day of relevant Committee meeting.
[2] Date of publication on the EMA public website.
[3] Last day of the month concerned.

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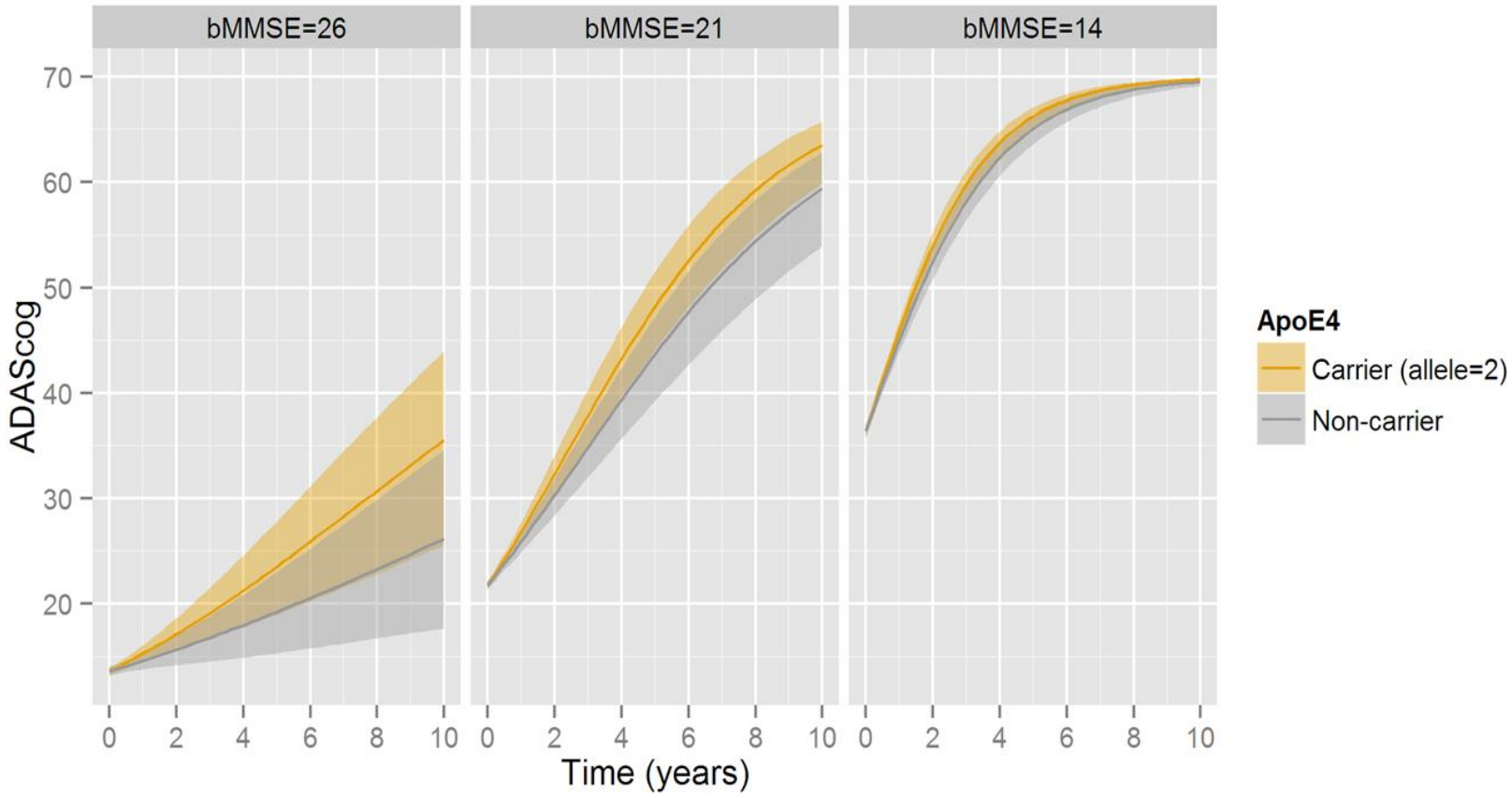
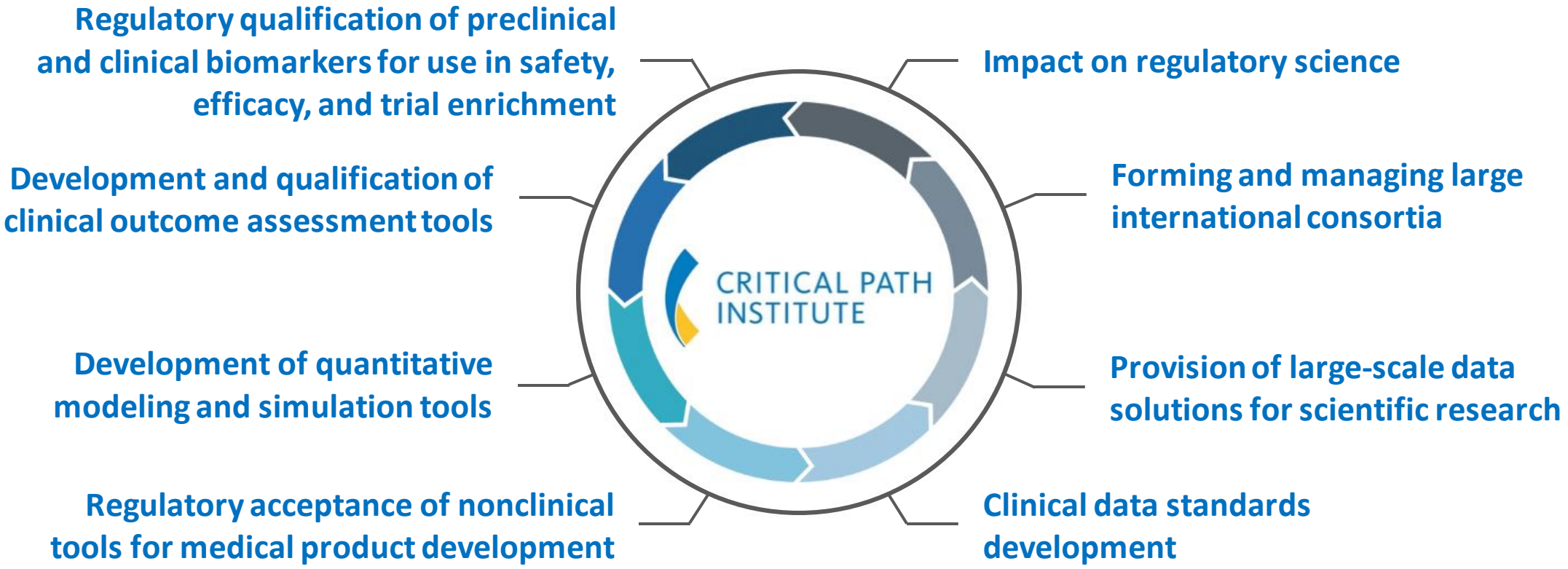


Disease progression: 75 year-old males, by APOE4 and baseline severity

THE CRITICAL PATH INSTITUTE

- **Host of over fifteen global, pre-competitive, public-private partnerships with participation from industry, academia, advocacy groups, and regulators, with impact on regulatory science**



C-PATH IS UNIQUELY FOCUSED ON DEVELOPMENT IN A PRE-COMPETITIVE ENVIRONMENT WITH SUPPORT OF INDUSTRY & REGULATORS

CRITICAL PATH INSTITUTE

Advanced Data Management

Extant technical expertise and infrastructure to obtain, integrate and make accessible high quality patient-level datasets suitable for queries and analyses

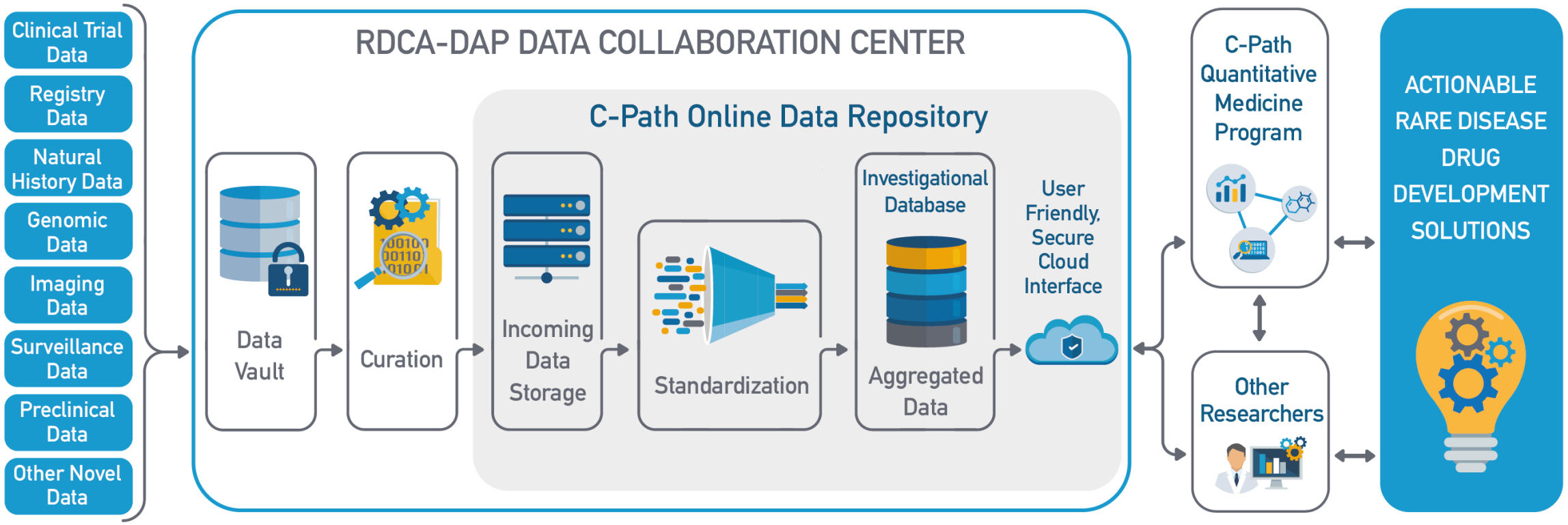
Advanced Analytics to Generate Solutions

Data-based ability to generate actionable and robust quantitative solutions across rare diseases

Focus on Drug Development

Potential to dramatically accelerate the evolution of the scientific understanding of rare diseases, reduce clinical trial costs, and thereby expedite drug development

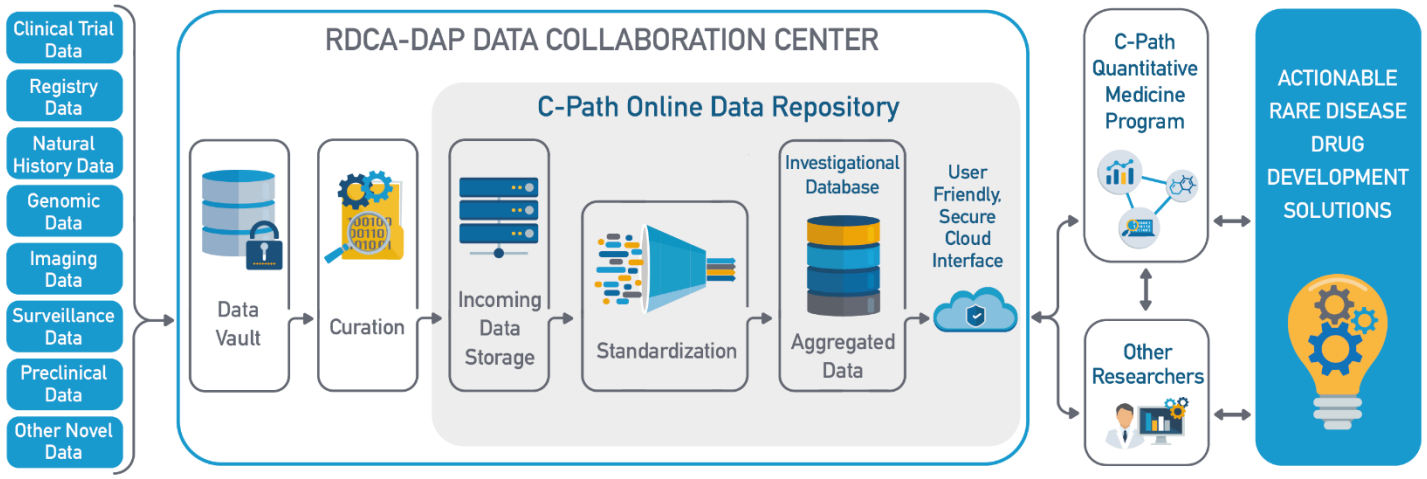
RDCA-DAP: A RESOURCE FOR THE FUTURE OF DRUG DEVELOPMENT IN RARE DISEASES



NORD® National Organization for Rare Disorders

CRITICAL PATH INSTITUTE

RDCA-DAP: A RESOURCE FOR THE FUTURE OF DRUG DEVELOPMENT IN RARE DISEASES



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NORD®
National Organization for Rare Disorders

- The combination of C-Path and NORD, with each group's expertise and vision, will establish the RDCA-DAP in order to facilitate disease-specific data sharing-informed disease characterization, at a quality level that will meet the development needs of industry and regulatory requirements

RDCA-DAP

- By creating the RDCA-DAP, the need for one-off disease characterization efforts for every disease will be eliminated
- Instead we have a living, durable structure ready to establish in rapid order a data sharing database for any given rare disease
  - Minimize start up time
  - Minimize development time
  - Minimize delivery time of new therapeutics to patients

EARLY SUCCESSES OF RDCA-DAP IN DATA SHARING

Commitments to sharing key patient-level data

- Friedreich's Ataxia Database
  - First data source for RDCA-DAP
- NORD's IAMRARE™ Registries
  - Soon to be integrated
- Who wants to be next?

SUMMARY

- **C-Path has an established track record and expertise in secure data sharing and integration**
  - RDCA-DAP poses an exciting opportunity to grow and expand those capabilities
- **NORD has an established track record and expertise in the generation of robust patient registries and patient outreach**
  - RDCA-DAP poses an exciting opportunity to continuously expand and optimize such registries
- **By working together, RDCA-DAP can transform the drug development landscape for rare diseases**

THANK YOU

A SUCCESS STORY – REGULATORY FIRSTS

CRITICAL PATH INSTITUTE

C-Path Regulatory Successes

Alzheimer's Disease
- AD clinical trial database
- FDA & EMA endorsed AD clinical trial simulation tool
- EMA qualified AD biomarker
- FDA & EMA letters of support
  - Biomarkers & MCI model

Parkinson's Disease
- FDA letter of support
  - PD biomarker
- EMA model-based qualified PD biomarker

Multiple Sclerosis
- EMA qualified Performance Outcome Measure*
  - Test battery for all forms of MS which could be used in conjunction with other performance measures and functional scales

* in public comment phase

Tuberculosis
- EMA qualified in-vitro platform
- Pathogen genomics data platform
- PB/PK Model for pulmonary drug distribution received scientific advice

Polycystic Kidney Disease
- EMA & FDA model-based qualified Total Kidney Volume (TKV) imaging biomarker
- FDA letter of support
  - TKV imaging biomarker
- PKD clinical database

Patient-Reported Outcomes
- FDA clinical outcome assessment qualification
  - Symptoms of Major Depressive Disorder Scale
  - Non Small Cell Lung Cancer Symptom Assessment Questionnaire
  - Asthma Daytime and Nighttime Symptom Diaries

Predictive Safety Testing
- EMA/FDA/PMDA qualified non-clinical kidney safety biomarkers
- FDA qualified clinical kidney safety markers
- FDA & EMA letters of support
  - Biomarkers (kidney, skeletal muscle injury, liver)

FDA U.S. FOOD & DRUG ADMINISTRATION
- 8 Qualification Decisions
  - Polycystic Kidney Disease
  - Predictive Safety Testing
  - Patient-Reported Outcome
- 1 Fit-for-Purpose Endorsement
- 7 Letters of Support

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
- 7 Qualification Decisions
  - Polycystic Kidney Disease
  - Tuberculosis
  - Alzheimer's
  - Predictive Safety Testing
  - Parkinson's
  - Multiple Sclerosis
- 7 Letters of Support

pmda 独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency
- 1 Qualification Decision
  - Predictive Safety Testing