Successful Modeling and Simulation in a Consortium: A Recipe for Success

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CLINICAL PHARMACOLOGY
Global Product Development

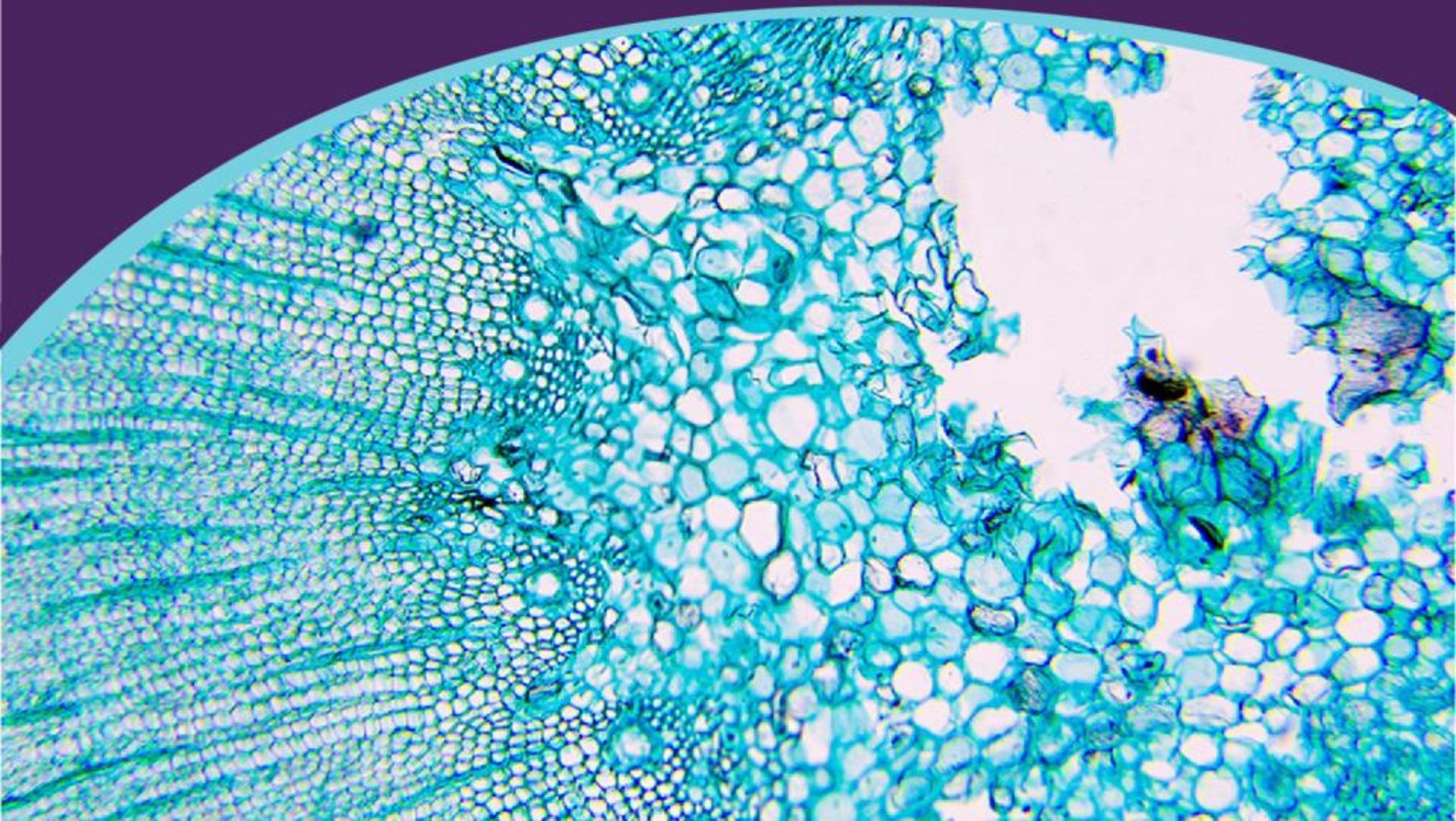
Conflict of Interest and Acknowledgements

- Brian Corrigan is an Employee of Pfizer
- Thanks to
  - Klaus Romero and Diane Stephenson (C-Path)
  - Jim Rogers and Marc Gastonguay (Metrum)
  - Kaori Ito and Haoyu Wang (Pfizer)
  - CAMD members

Outline

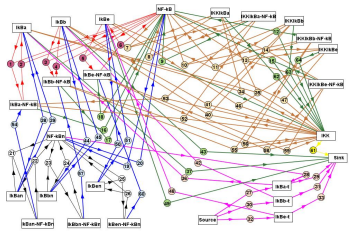
- Why a Consortia Approach to MIDD and DDT Tools Makes Sense
- Leverage Past Consortia Success
  - Contrast CAMD /HD-RSC to demonstrate Consortia Approach to DDT
    - A Clear Plan
    - Data Standards
    - Clear Context of use
    - Pre specification of work
    - Prioritization
    - Regulatory Path(s) for acceptance
    - Tools (not models)

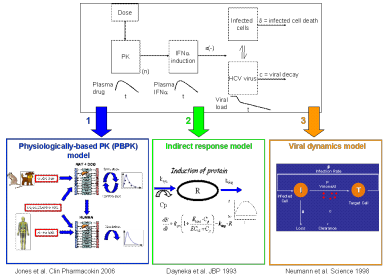
Developing a DDT in A Consortium: Why?

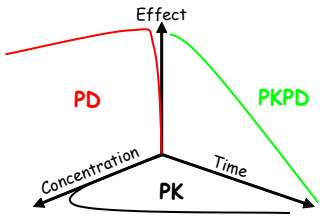


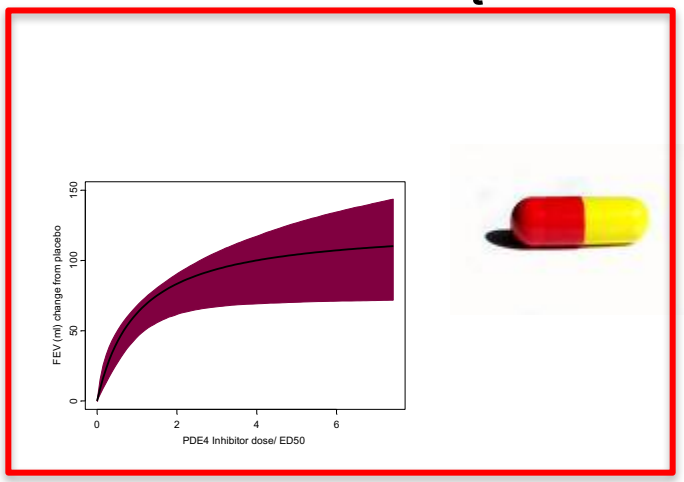
MIDD is used End-to-End in R&D

Pathway	Target	Drug & pharmacology	Benefit/Risk	Effectiveness & Reimbursement









Systems Biology	Systems Pharmacology	Preclinical PK-PD	Clinical PK-PD & disease modeling	Outcome & commercial M&S

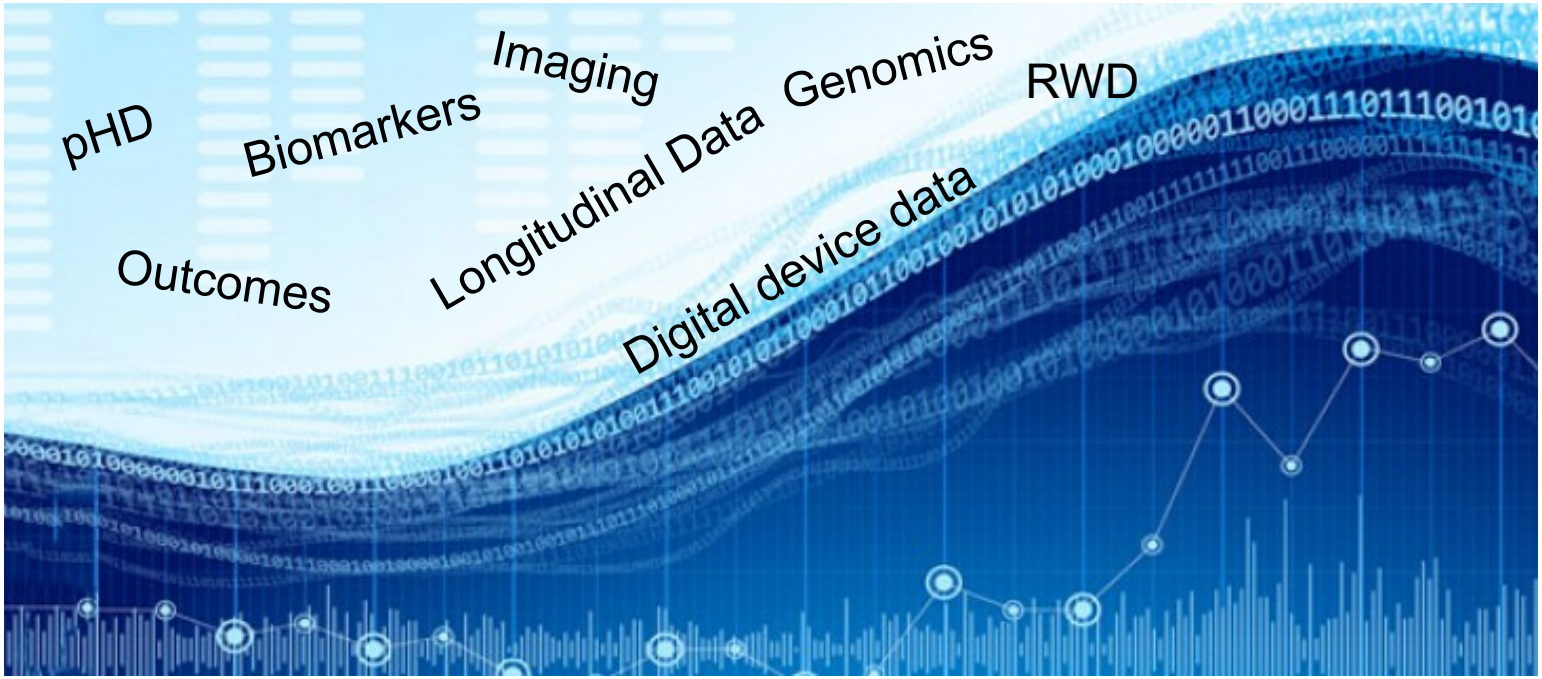
'Right target' ***'Right molecule'*** ***'Right trial & dose'***

'Right pathway'

MIDD

'Right patients'

The Data Tsunami



DATA >> resources to interrogate/understand it

(bigger than individual organizations can make or maintain)


OLD WAY
NEW WAY

Growth of Shared "Generally Accepted" DDT Solutions

Model for a disease platform and/or group of targets

Disease progression and patient characterization in Alzheimer, diabetes, rare disease, etc

Precompetitive development of Systems Pharmacology Models (eg immunogenicity)

Model for a standard molecule

Itraconazole PBPK model

Model/strategy for a clinical pharmacology area

TQT Study Waivers

Pediatric Strategy

Labeling for Special Population


The Journal of Clinical Pharmacology

Original Manuscript

Utility of Model Based Approaches for Informing Dosing Recommendations in Specific Populations: Report from the Public AAPS Workshop

Islam R. Younis PhD[1,*], J. Robert Powell PharmD[2], Amin Rostami-Hodjegan PharmD, PhD[3], Brian Corrigan PhD[4], Norman Stockbridge MD, PhD[5], Vikram Sinha PhD[6], Ping Zhao PhD[1], Pravin Jadhav PhD, MPH[7], Bruno Flamion MD, PhD[8] and Jack Cook PhD[4]

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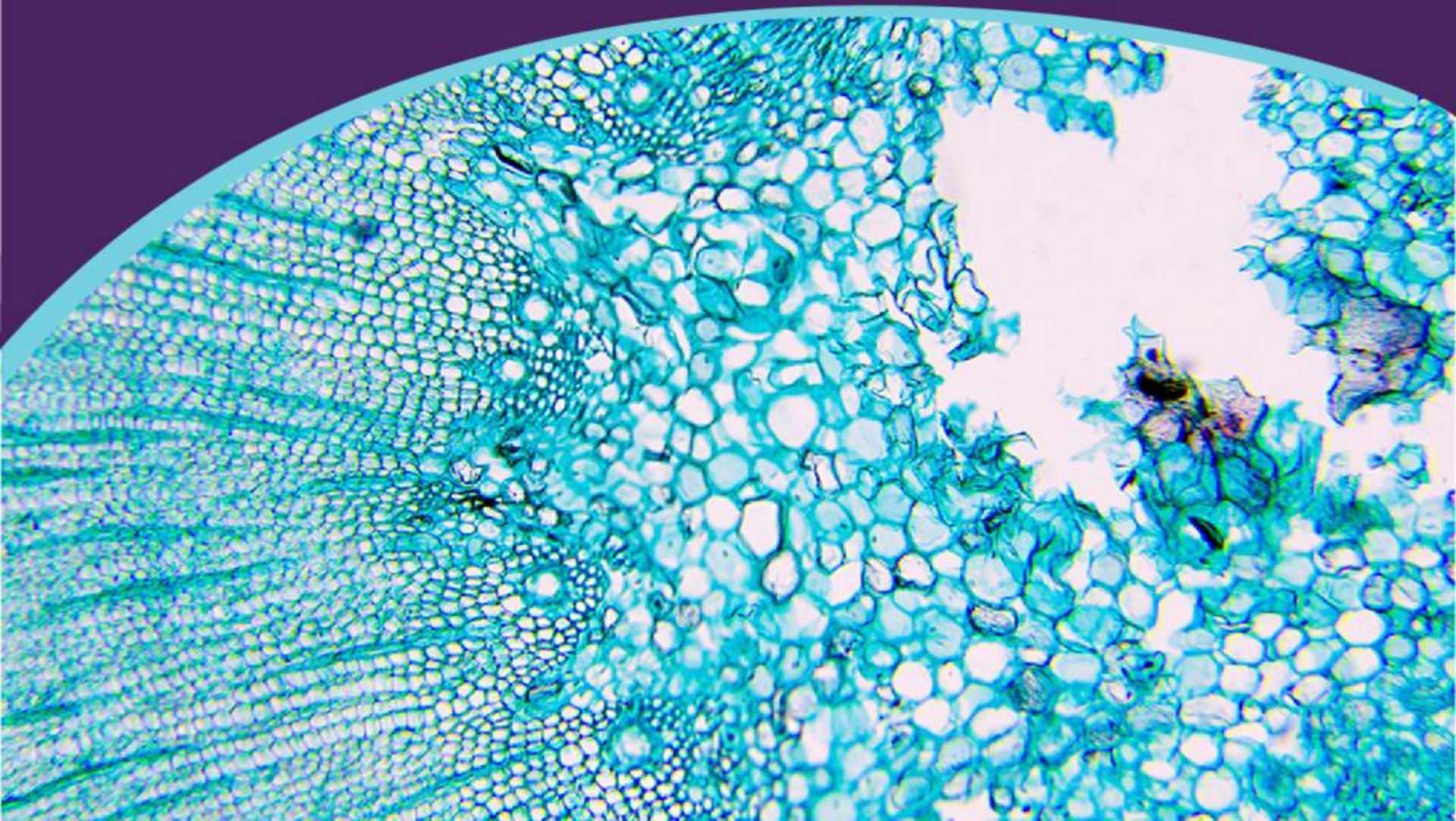
Issue

The Journal of Clinical Pharmacology

Accepted Article (Accepted, unedited articles published online and citable. The final edited and typeset version of record will appear in future.)

A Recipe for Success in a DDT Consortia



1 TEASPOON OF IDEAS

½ CUP OF GOODWILL

1 PINCH OF POSITIVITY

¾ CUP OF IMAGINATION

1 LB OF LEADERSHIP

2 SPOONFULS OF TEAMWORK

3 TABLESPOONS OF CHALLENGE

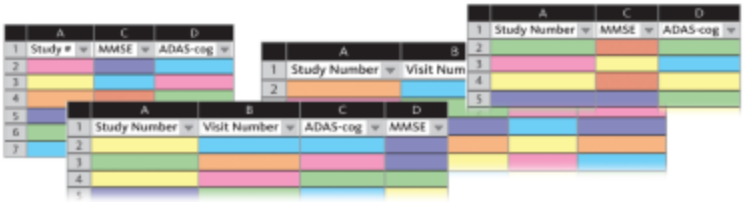
Serve warm with a large helping of patience

The DDT Consortia Recipe

1	*Tonne* of good ideas
500	*mbq* of “radiant enthusiasm”
XVI	*stone* historical data
1/2	gallon (imp) of new biomarkers
0.487	L of sweat
47.8	g of good luck
1	New York second to complete

Defined as the time between a green light and a cab honking in NYC (aka the shortest unit of time in the multiverse)

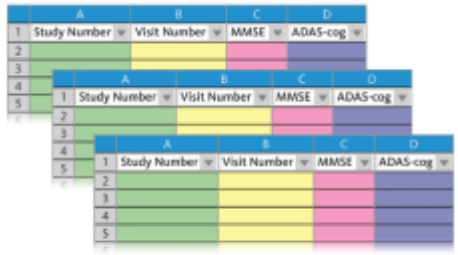
Data Standards



Disparate Legacy Data

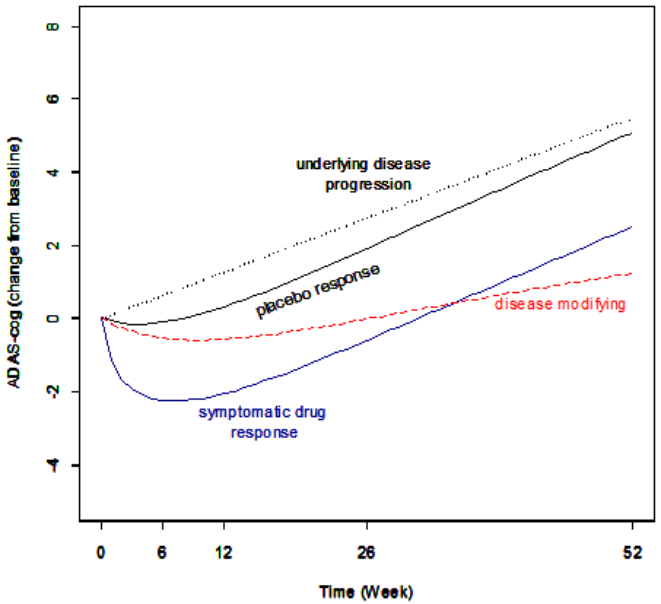
CDISC Data Standards

Multiple year journey to get standardized Data (legal, ethics, standards)



Integrated Data

Deterioration



Romero K, et al. Striving for an integrated drug development process for neurodegeneration: The Coalition Against Major Diseases. Neurodegen Dis Manage 2011;1(5): 379-85.

Data Standards *ACCELRATE CURES*

CHDI FOUNDATION

Accelerating therapeutic development for Huntington's disease

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September 11, 2017

C-Path, CHDI Foundation, and CDISC Announce Public Review Period for Huntington's Disease Therapeutic Area User Guide

TUCSON, AZ, NEW YORK, NY, and AUSTIN, TX – September 11, 2017 – Critical Path Institute (C-Path), CHDI Foundation, Inc. (CHDI), and The Clinical Data Interchange Standards Consortium (CDISC) announce the availability of a draft Huntington's disease (HD) Therapeutic Area User Guide (TAUG-HD v1.0) for public review. The TAUG-HD v1.0 describes how HD clinical data should be recorded in a standardized database to establish common best practices across the healthcare industry for the recording, reporting, and sharing of clinically relevant disease-specific metadata, research data, and patient information. Use of the standard will allow the HD research community to compare and contrast data from different studies more easily and with more scientific rigor, and will make it easier for researchers to understand natural history, biomarker, and trial data in the future. It will also facilitate regulatory submissions for novel therapeutics.

A Clear Plan

2. HD Modeling Working Group

This working group will be responsible for developing a quantitative clinical trial enrichment platform, based on a comprehensive disease progression model for manifest HD. This group will also lead subsequent modeling efforts, based on available data and specific needs in HD drug development. This effort will include the development of a clinical trial simulation tool, based on the expansion of the HD drug disease trial model with inclusion of a placebo effect model, a drug effects model, and a drop-out model for manifest stages of HD. Both, the quantitative clinical trial enrichment platform and the clinical trial simulation tool are intended to be submitted for regulatory acceptance.

Goals:

- Develop and implement a modeling analysis plan for a comprehensive disease progression model, including proposed context-of-use, based on a survey of existing HD models. The initial focus will be a model-based clinical trial enrichment tool aimed to optimize the clinical trial design.
  - Coordinate and lead face-to-face meetings with regulators based on modeling submissions.
  - Consider pursuit with additional regulatory agencies.
- Develop and deliver on an HD-RSC publication strategy to communicate modeling and simulation achievements.

Outlines the specific questions we want to answer and what data we need to answer them

Clear Context of Use Example

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

General Area: A model-based clinical trial enrichment platform to help inform, through simulations, the definition of inclusion/exclusion criteria, enrichment strategies and stratification approaches for Phase II and Phase III studies evaluating therapeutic candidates for MCI.

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).

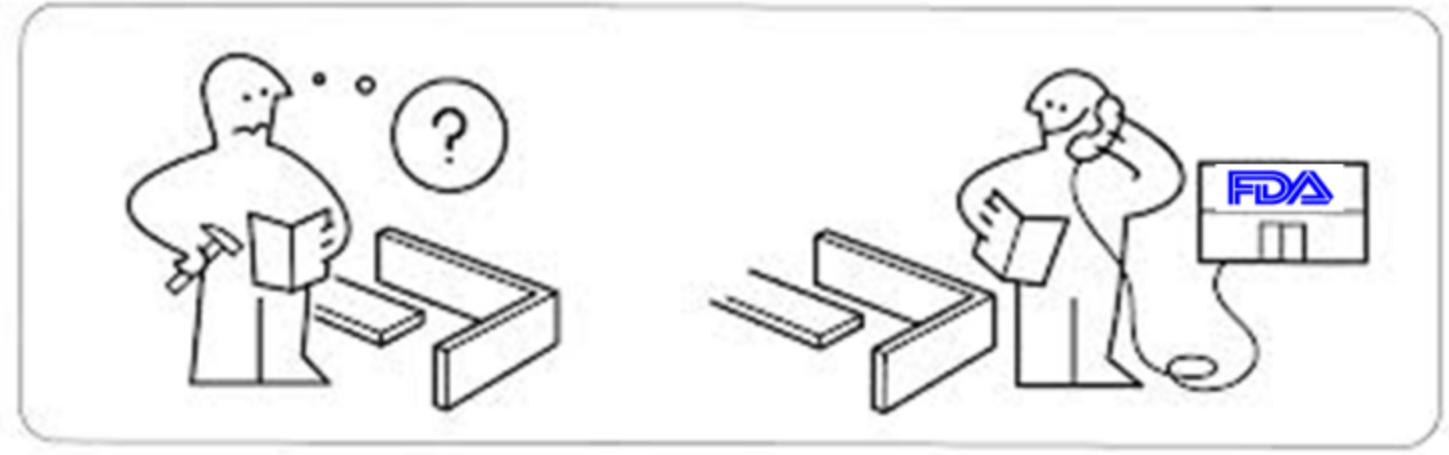
Stage of Drug Development for Use: Phase II and III clinical stages of MCI drug development.

Intended Application: Simulations based on this platform will allow development teams to inform the definition of subject selection, entry criteria, enrichment strategies and stratification approaches for Phase II and Phase III studies evaluating therapeutic candidates for MCI, by helping to define sub-population progression rates in CDR-SB over the course of the trial.

Aligns Consortia, Workgroup, Collaborators, HAs around the Objective/Scope
Defines Data Requirements and Potential analyses that may be required

Socialize the Context of Use

- To All Stakeholders
  - Is it useful?
    - Does it answer your questions
- As early as possible
  - Avoids surprises/rework



Have Clear Logical Priorities

The **specific aims** for the first phase of the HD-RSC are to establish:

i) Clinical Data Standards: Finalize development of consensus clinical data standards (CDISC format) and ensure their dissemination to the HD research community.

ii) HD Trial/Study Database: Create a secure online HD Database of integrated, CDISC-standardized patient-level clinical trial and observational study data, accessible to qualified researchers.

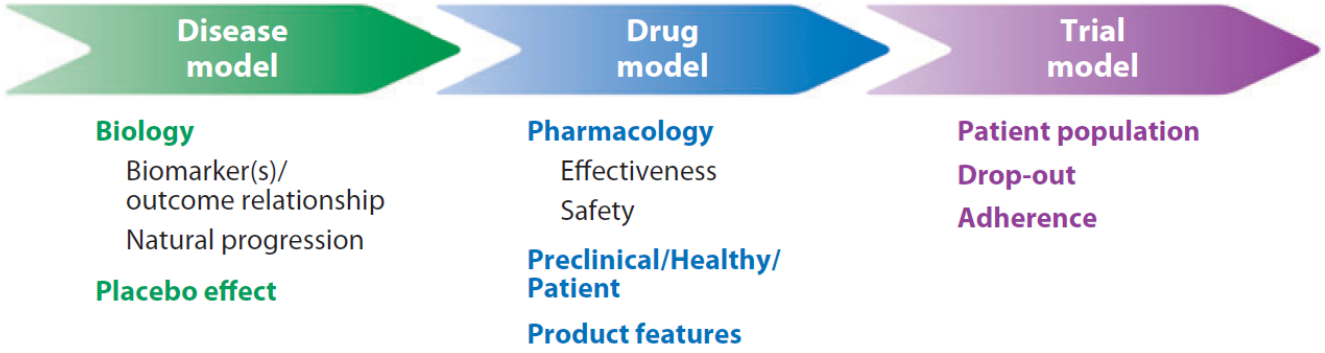
iii) HD Progression Model: Apply modeling and computational analysis strategies to the unified HD Database to develop a comprehensive quantitative model of disease progression at defined stages of HD.

iv) Quantitative Drug Development Tool: Achieve formal regulatory acceptance of a Quantitative Drug Development Tool for Clinical Trial Enrichment, based on the HD progression model.

v) Quantitative Trial Model: Develop a quantitative drug/disease trial model for manifest HD.

vi) Clinical Trial Simulation Tool: Achieve formal regulatory acceptance of a Clinical Trial Simulation Tool, based on the trial model, to support efficient design of HD clinical trials.

What is Disease Progression Modeling?



- the progression in time of a disease in an individual is represented as a mathematical function.
- Initially, a model is produced that characterizes a given disease's time profile in the absence of therapeutic intervention; this is a base model.
- Changes due to active treatment are superimposed onto the base model to simulate the effect on the disease of a drug.
- Disease progression models offer greater insight into data obtained from clinical trials, allowing for better study designs.
  - Use multiple time points vs endpoint analysis

Disease Drug Progression Model in Clinical Trial

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

S_0 : baseline disease "state"

S(t): expected "state" at a time "t"

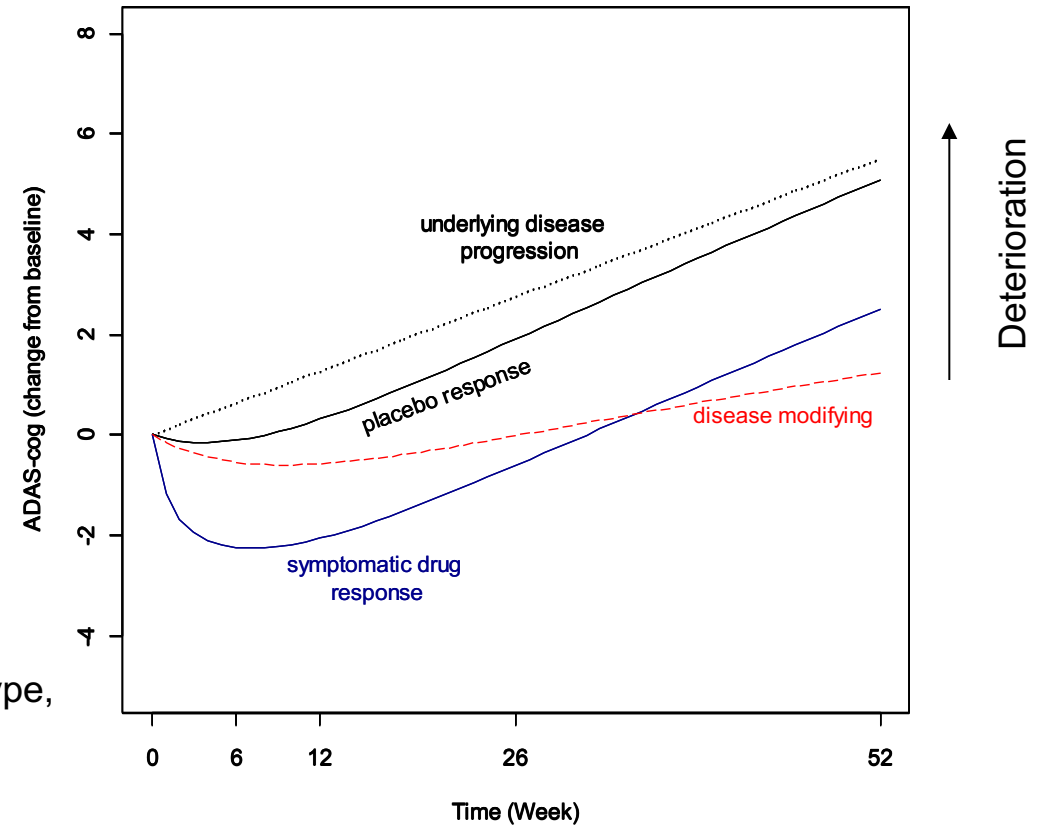
α : disease progression rate

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):

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

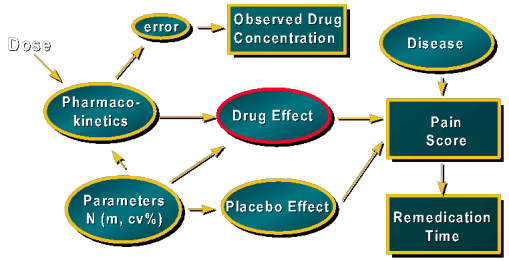
..or combination with symptomatic effect

DDT and Trial Simulations: Optimize Study Desgin

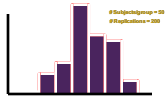
Evaluate "what if" scenarios……

Run Multiple
Replications of Trial

DDT Model



Range of Outcomes



Statistics

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

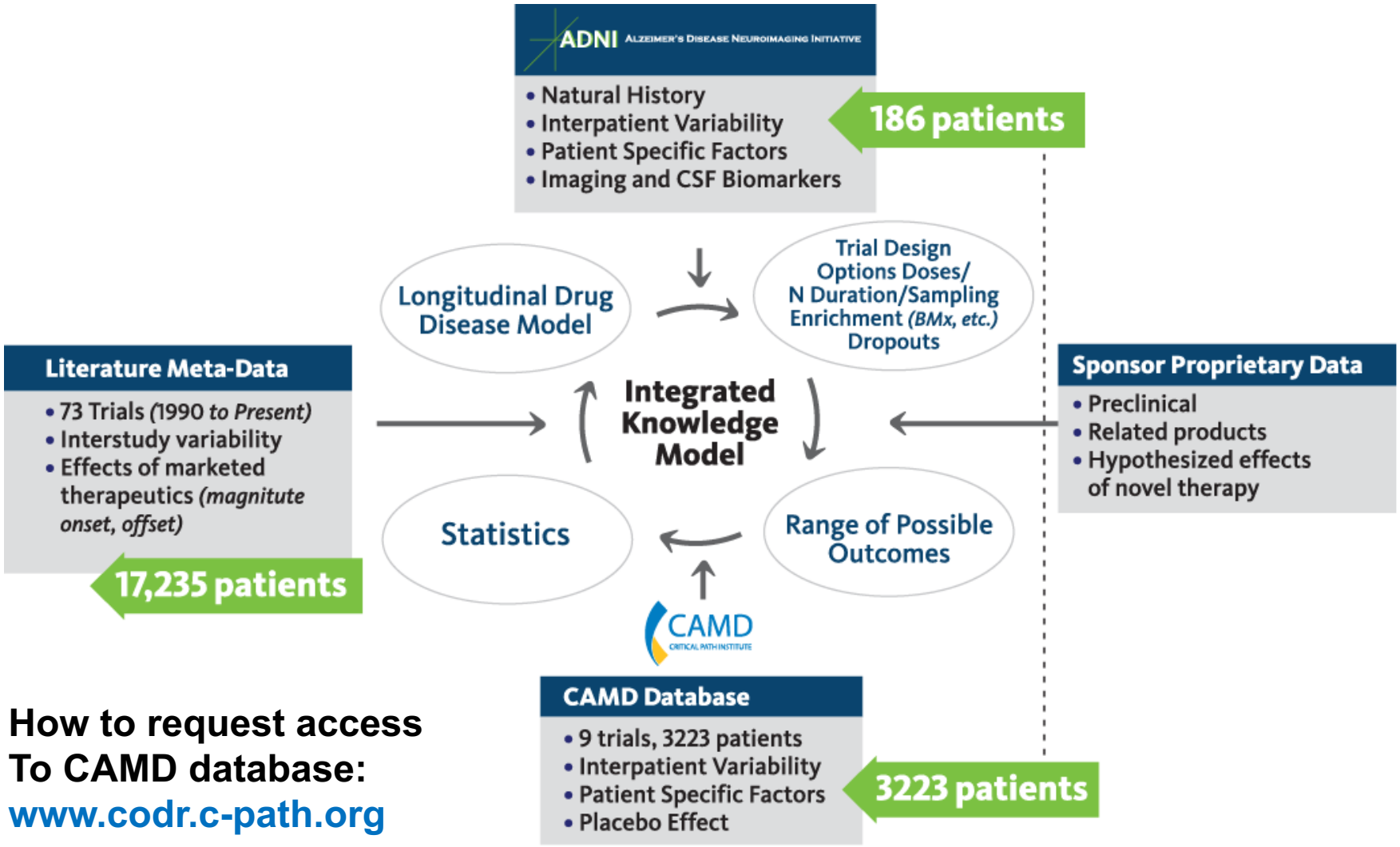
Trial Designs

- 5 possible doses
- Explore different N

Modify Design

AD Drug-Disease-Trial Model

Integrating the Clinical Trialist's World



How to request access To CAMD database:
www.codr.c-path.org

A Clear Pathway For Acceptance of Community DDTs

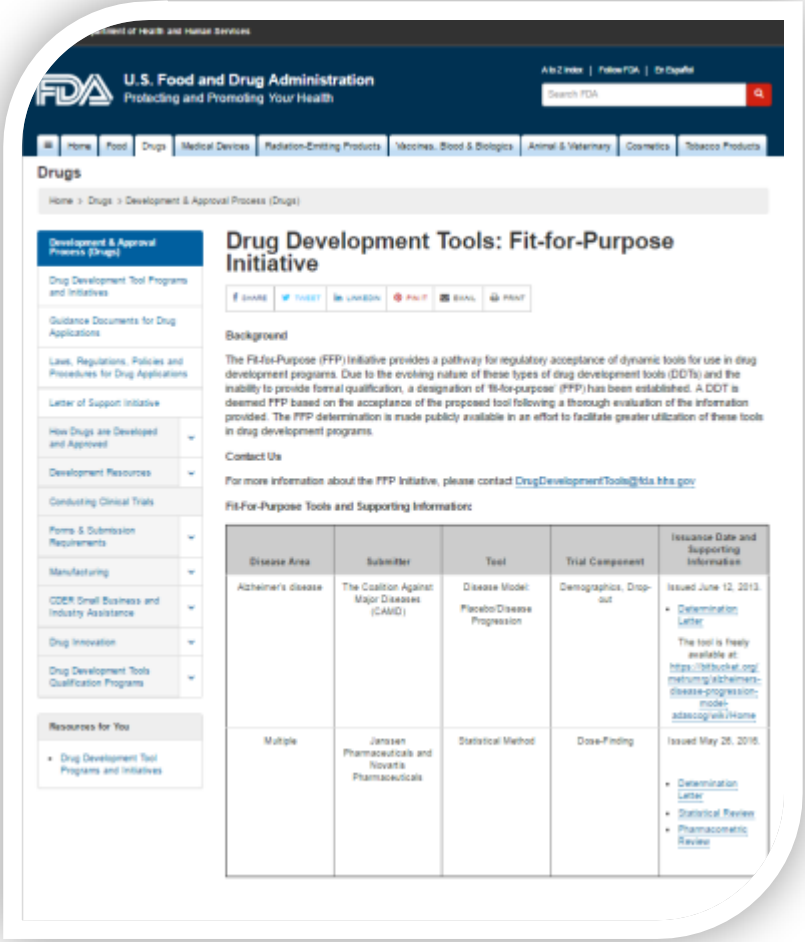
C-Path/FDA pioneered the pathway for Regulatory acceptance of Model Based DDTs

Modeling & Simulation for Medical Products Workshop
September 26, 2013

SHORT REPORT

Modeling and simulation for medical product development and evaluation: highlights from the FDA-C-Path-ISOP 2013 workshop

Klaus Romero · Vikram Sinha · Sandra Allerheiligen · Meindert Danhof · Jose Pinheiro · Naomi Kruhlak · Yaning Wang · Sue-Jane Wang · John-Michael Sauer · J. F. Marier · Brian Corrigan · James Rogers · H. J. Lambers Heerspink · Tawanda Gumbo · Peter Vis · Paul Watkins · Tina Morrison · William Gillespie · Mark Forrest Gordon · Diane Stephenson · Debra Hanna · Marc Pfister · Richard Lalonde · Thomas Colatsky

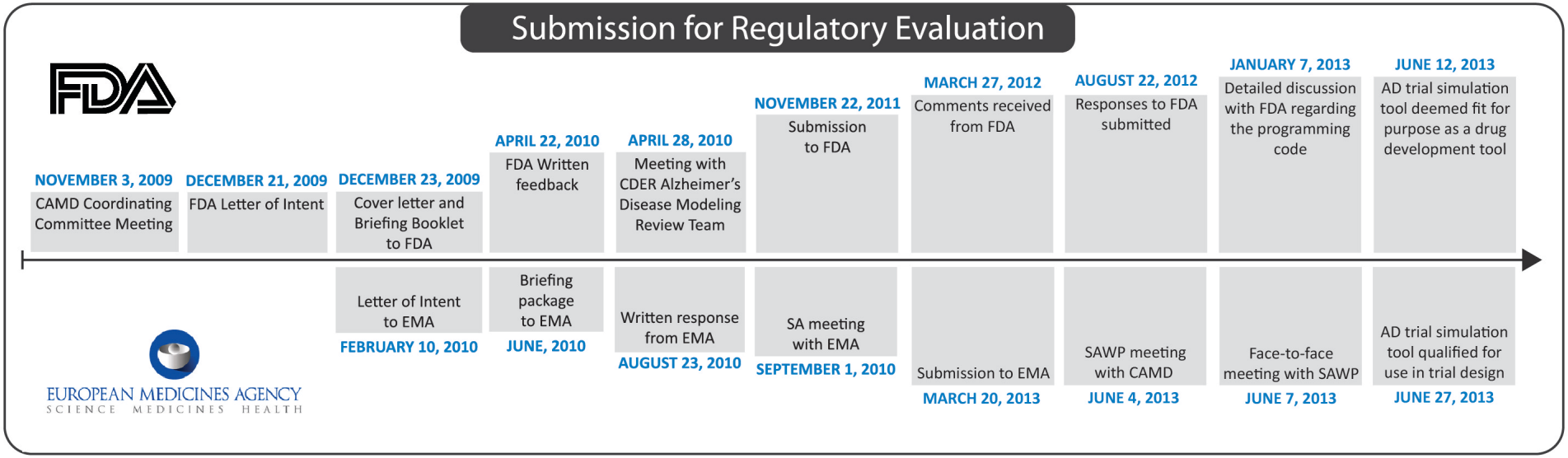


http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm

The Regulatory Journey

The total journey took 1317 days *(3 years, 7 months and 9 days).*

- On June 12, 2013 the FDA determined the CTS tool was "Fit for Purpose."
- On September 19, 2013 the EMA determined the CTS tool was "Qualified for Use."



Interactive Web Application for Clinical Trial Simulation and Reporting: R Shiny with 'adsim' Package for Model-based Simulation in Alzheimer's Disease

Haoyu Wang[1],Dan Polhamus[2], Jim Rogers[2], Klaus Romero[3], Puneet Gaitonde[4], Brian Corrigan[4] and Kaori Ito[4]

[1]Department of Statistics, North Carolina State University, Raleigh, NC; [2]Metrum Research, Tarrifville, CT; [3]Critical Path Institute , Tucson, AZ; [4]Pfizer Inc., Groton, CT

OBJECTIVES

An open-source web-based Alzheimer's Disease (AD) trial simulation application was developed using the R packages "shiny" and "adsim". The app allows for simulation, visualization and reporting of simulation results of common AD trial designs utilizing ADAS-cog, a common measure of cognition used as a primary endpoint in AD clinical trials. The tool is designed for all users in a clinical development team, including individuals without knowledge in R.

RESOURCES

Hosted Application: https://isop.shinyapps.io/Alzheimer/ . Source Code: https://github.com/why94nb/shiny-app-for-adsim/ .

METHODS

Individual and summary level data from AD patients was used to develop a longitudinal disease Progression model,

which was then developed as an R Package (adsim) for trial simulation in mild and moderate AD. Using adsim and shiny, an open-source R based application suitable for use by members of a drug development team was developed. The code is maintained in an open source repository to allow for ongoing use/upgrade by anyone.

RESULTS

The app consists of six tabs that allow the user to set up, run, and view results from the simulation. The "About" tab contains information about the "adsim" package and a user guide for the app. Users can choose various trial design and drug effects in the "Simulation Set Up" tab. Spaghetti plots and figures about baseline information (gender, age, ApoE and MMSE) are available in the "Illustrative Statistics (Test)" tab and can be downloaded. A test statistics summary is shown in the "Simulation Summary" tab. In addition, patient tables(Both baseline information and longitudinal table) are downloadable for further analysis and the user can also download. A short report summarizing parameter settings and all the outputs generated during the simulation is also available.

CONCLUSIONS

We have developed an open-source R shiny app to allow development team members to perform Alzheimer's Disease clinical trial simulation, utilizing an reproducible way to visualize simulation results and to share the results within the clinical team (clinical pharmacology, statistics and clinicians) .

Journal of Pharmacokinetics Pharmacodynamics (ACOP W-27, 2016

We Have Great Ingredients…..

- Skilled and Knowledgeable team
  - Both in HD and in Consortia
- Previous Consortia Experience
- Rich Data Sources
  - Understanding of importance of Data standards
- Clear understanding of the Disease
  - Emerging CGT approaches to therapy
- Innovative analysis techniques/tools available
- Clear Regulatory Path
- Patients waiting for us