A Comprehensive Clinical Trial Simulation Tool for Alzheimer's Disease: Lessons for Model Collaboration

Dr. Brian Corrigan (Pfizer Global Research),
On behalf of the CAMD M&S Workgroup,
September 26, 2013, Washington DC

CAMD Mission

Mission: <u>to develop new technologies and methods to accelerate the development and review of medical products for neurodegenerative diseases</u> through 1) (1) qualification of biomarkers, (2) development of common data standards, (3) creation of integrated databases for clinical trials data, and **<u>(4) development of quantitative model-based tools for drug development.</u>**

CAMD: Modeling Work Group Mission (Feb 2009)

- To develop a quantitative model to describe the progression of cognitive changes in mild to moderate to test and optimize operating characteristics of trial designs for AD (via simulations based on the model).
- To submit the results of the analyses to regulatory agencies for review and qualification for potential use (as, defined by the "Context of Use) to aid study design for teams involved in AD drug development"
- Deliverables of a submission package for review, and tools, code and datasets for development team use

Pathways Used

CAMD
CRITICAL PATH INSTITUTE

FDA

Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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) Shaniece Gathers, 301-796-2600.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical

EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2010
EMEA-H-4260-01-Rev. 6

European Medicines Agency Guidance for Companies requesting Scientific Advice and Protocol Assistance

This guidance document addresses a number of questions that users of the Scientific Advice or Protocol Assistance procedures may have.

It provides an overview of the procedure to obtain Scientific Advice or Protocol Assistance and gives guidance to companies in preparing their request. This guidance document also explains the scope and nature of Scientific Advice and Protocol Assistance. It will enable companies to submit requests which are in conformity with Scientific Advice Working Party (SAWP) requirements and which can be validated and evaluated quickly and efficiently.

Furthermore, companies will be guided through the different steps of the procedure and receive useful information on the preparation of a possible discussion meeting with the SAWP.

This guidance document is updated regularly to reflect new developments and include accumulated experience.

In particular, this version was amended to include:

- the possibility of scientific advice on changing the classification for the supply of a medicinal product (reclassification of Legal Status), Q3
- clarification of the collaboration between SAWP and PDCO for products undergoing scientific advice, Q5
- the possibility of parallel CHMP scientific advice/protocol assistance and advice from Health Technology Assessment bodies, Q25
- the European Medicines Agency's (hereafter referred to as the Agency or the EMA) new corporate identity
- the introduction of a briefing document template
- updated fees

Instructions for users

To obtain information on a certain topic, simply click on the highlighted keyword. We trust that the information linked to the keyword should answer most of your queries.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

AD Modeling Team and Journey to Success

- The total journey took 1317 days *(3 years, 7 months and 9 days).*
- On June 12, 2013 the FDA determined the modeling and simulation tool was “Fit for Purpose.”
  - This was the language chosen since the term “Qualification” was felt by FDA to be more appropriate to a biomarker.
  - This was the first FDA recognition of a “qualification” package for CAMD and the first clinical “qualification” for the Critical Path Institute.
- EMA Favorable Scientific Advice July, 2013

The Model

J Pharmacokinet Pharmacodyn (2012) 39:479–498
DOI 10.1007/s10928-012-9263-3

ORIGINAL PAPER

Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a beta regression meta-analysis

James A. Rogers · Daniel Polhamus · William R. Gillespie · Kaori Ito · Klaus Romero · Ruolun Qiu · Diane Stephenson · Marc R. Gastonguay · Brian Corrigan

A Comprehensive Clinical Trial Simulation Tool for Alzheimer's Disease: Lessons for Model Collaboration?

Dr. Brian Corrigan (Pfizer Global Research),
On behalf of the CAMD M&S Workgroup,
September 26, 2013, Washington DC

WHAT WAS COMPREHENSIVE FROM THE MODEL APPROVAL CONTEXT?

A COMPREHENSIVE TEAM…..

With Broad Input Across Disciplines and Partners…

AD Modeling Team Members:

Klaus Romero
Brian Corrigan
Kaori Ito
Jim Rogers
Dan Polmamus
Richard Meibach
Richard Mohs

Yaakov Stern
Lon Schneider
Gary Cutter

Yaning Wang
Vikram Sinha
Li Zhang
Marc Walton
Nick Kozauer
Issam Zineh

Maria Isaac
David Brown
Jean Georges
Spiros Vamvakas
Robert Hemmings
Luca Pani

Special thanks to Bill Thies (Alz Asstn), Eric Sokol (AFA)

WITH A CLEARLY DEFINED AND AGREED CONTEXT OF USE

Context of Use Summary

What the tool is:

- A clinical trial simulation tool to help optimize clinical trial design for mild and moderate AD, using ADAS-cog as the primary cognitive endpoint

What it is based on:

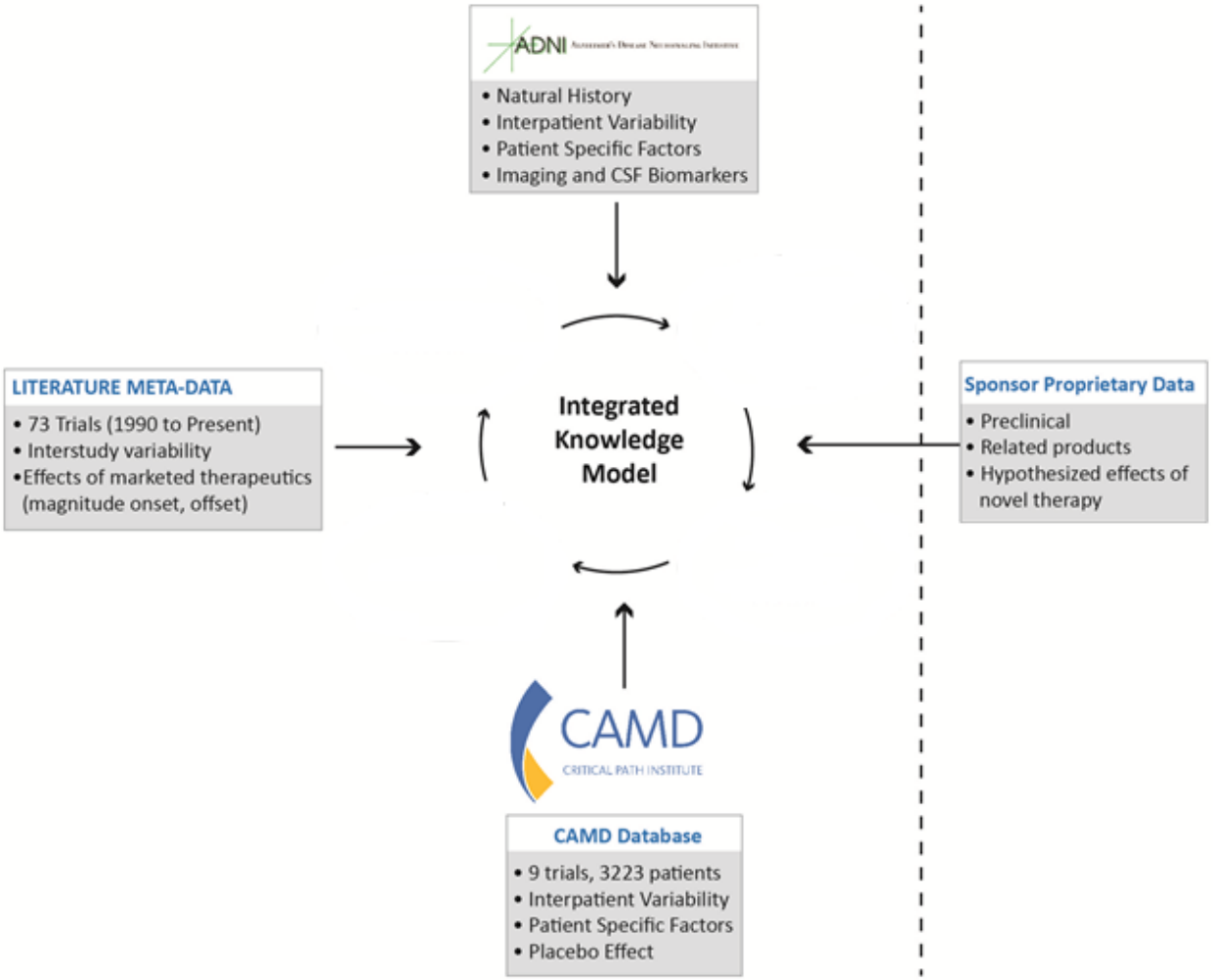
- A drug-disease-trial model that describes disease progression, drug effects, dropout rates, placebo effect, and relevant sources of variability

What it is NOT intended for:

- Approve medical products without the actual execution of well conducted trials in real patients

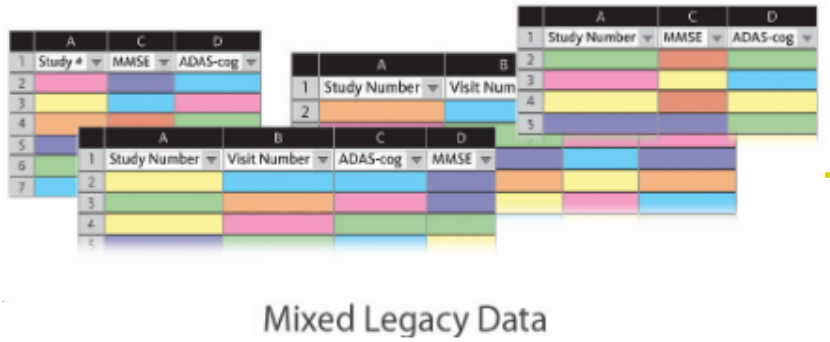
UTILIZING COMPREHENSIVE DATA

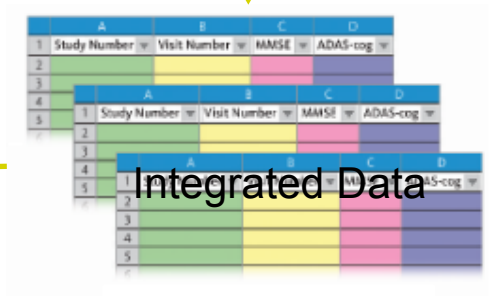
From All Relevant Sources



SCORED IN A STANDARDIZED MANNER…..

Data Standardization





Model Development

WITH A COMPREHENSIVE MODEL THAT BUILDS ON THE WORK OF OTHERS……

Tool Incorporates and Builds on Key Learning's from Multiple Researchers

CAMD
CRITICAL PATH INSTITUTE

Model	Drug Effect Component	Trial Components	Data Source	Covariates	linearity
Holford. Historical	Yes	Varied	Individual studies (tacrine)	Varied	Linear
Ito Literature	Yes (symptomatic agents estimated)	Placebo (onset and magnitude)	All controlled studies in the literature 1990-2008	Baseline severity	Linear (non-linearity introduced by baseline covariates)
Ito ADNI	No (NA)	No (NA)	ADNI (normal, MCI, mild AD)	Baseline severity Age, ApoE4 genotype, and sex	Linear (non-linearity introduced by baseline covariates)Fits normal MCI and mild AD
Samtani ADNI	No (NA)	No (NA)	ADNI Mild AD	disease onset, hippocampal volume and ventricular volume, age, total cholesterol, APOE ε4 genotype, trail making test (part B) score,	Nonlinear Fits mild AD
Faltaos et al	No	Drop-out No Placebo		Covariates influencing the intercept were baseline ADAS-cog score (did not use data prior to 4 months) and baseline Mini Mental State Exam score. No covariates influenced the disease progression slope	Nonlinear (log transform not suitable for whole range of ADAS-cog scores of 0-70).

Logit function to restrict ADAS-cog to its 0-70 range

$$\theta_{ipk} = \mathrm{E}\left[{}^{ADAS_{ipk}}/_{70} \,\middle|\, \mathrm{patient}_p\right]$$

$$g(\theta_{ipk}) = \eta_{pk} + \alpha_{pk} \times t_{ipk} + E_{\mathrm{PBO}}(t_{ipk}) + E_{\mathrm{DRG}}(t_{ipk}, D_{ipk})$$

Covariate: bMMSE

Distribution for survival analysis

Bateman function: placebo effect disappears as a function of time

$$T_{pk} \sim \mathrm{Weibull}(\alpha, h_{pk})$$

$$log(h_{pk}) = \beta_{\mathrm{Study},k} + \beta_1(bMMSE_{pk} - 21) + \beta_2(bAge_{pk} - 75)$$

Covariates: bMMSE, APOε4 status, age, gender

Survival coefficient

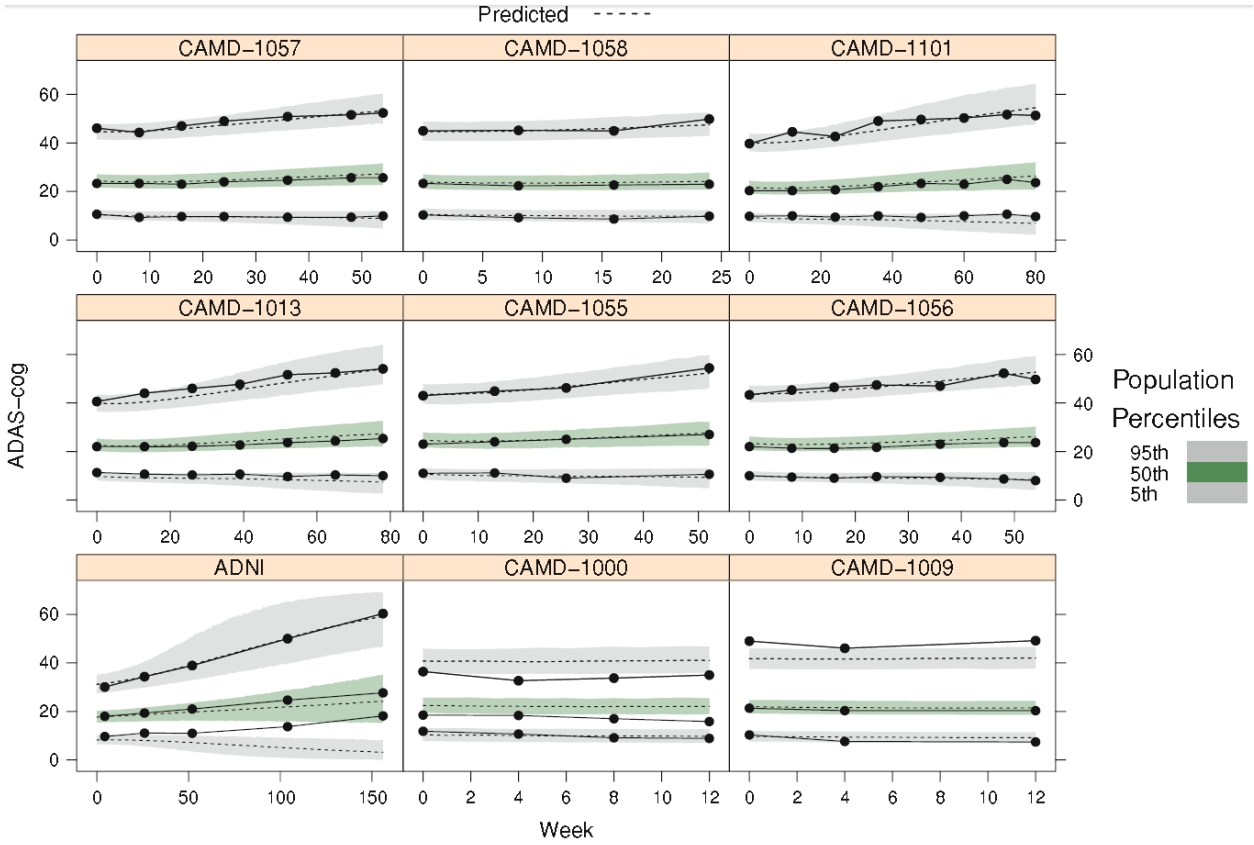
Baseline severity coefficient

Symptomatic / "DM" effects individually or combined

Age coefficient

SUPPORTED WITH INTERNAL PREDICTIVE CHECKS……

Tool Has Undergone Rigorous Predictive Check Procedures



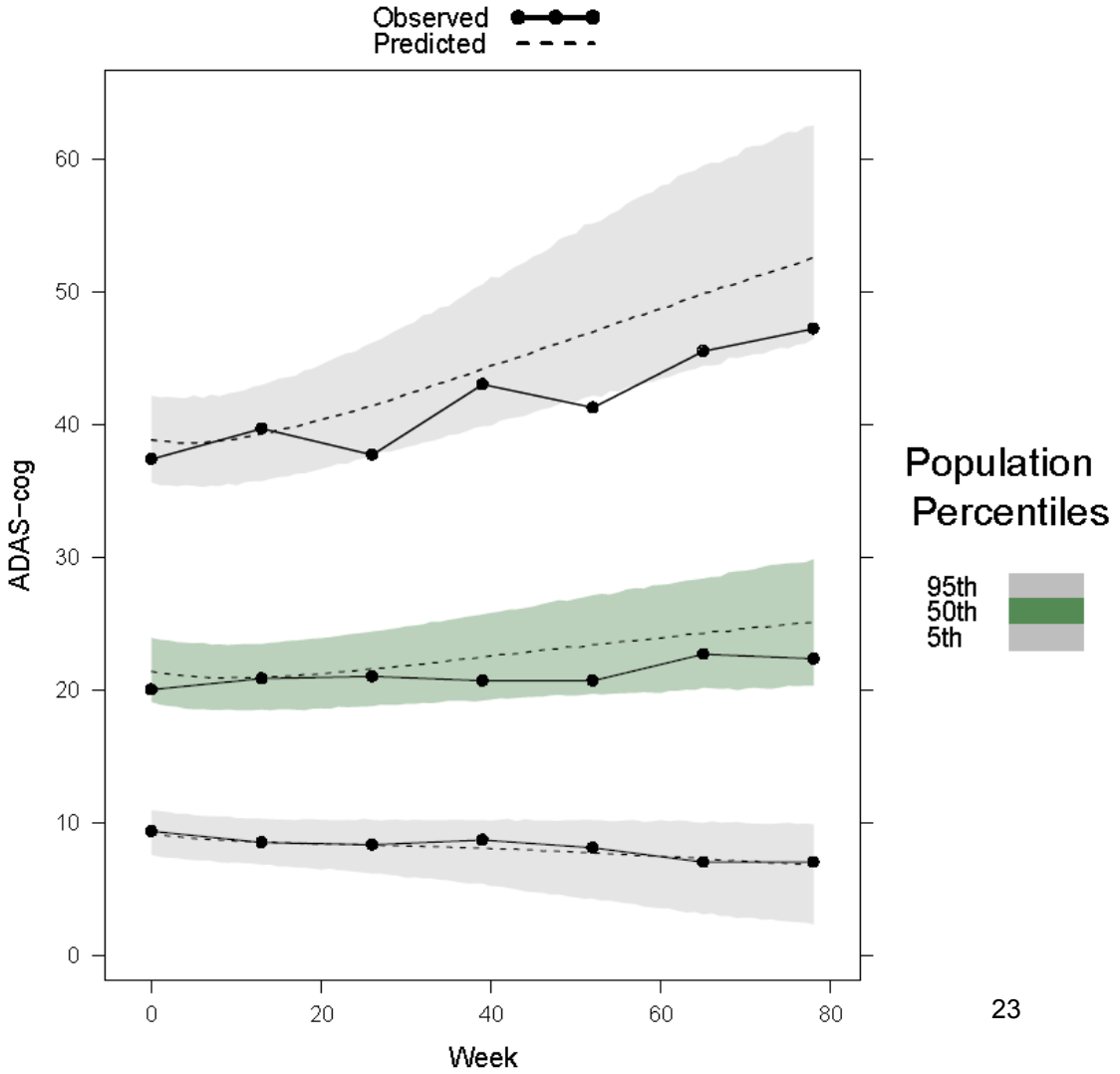
Unconditional predictive checks for sample population percentiles of ADNI and CAMD studies. The model adequately fits the data

AND EXTERNAL VALIDATION .....

Tool Further Validated With Using Data From External Dataset

Patient-level control arm data from study 1014:

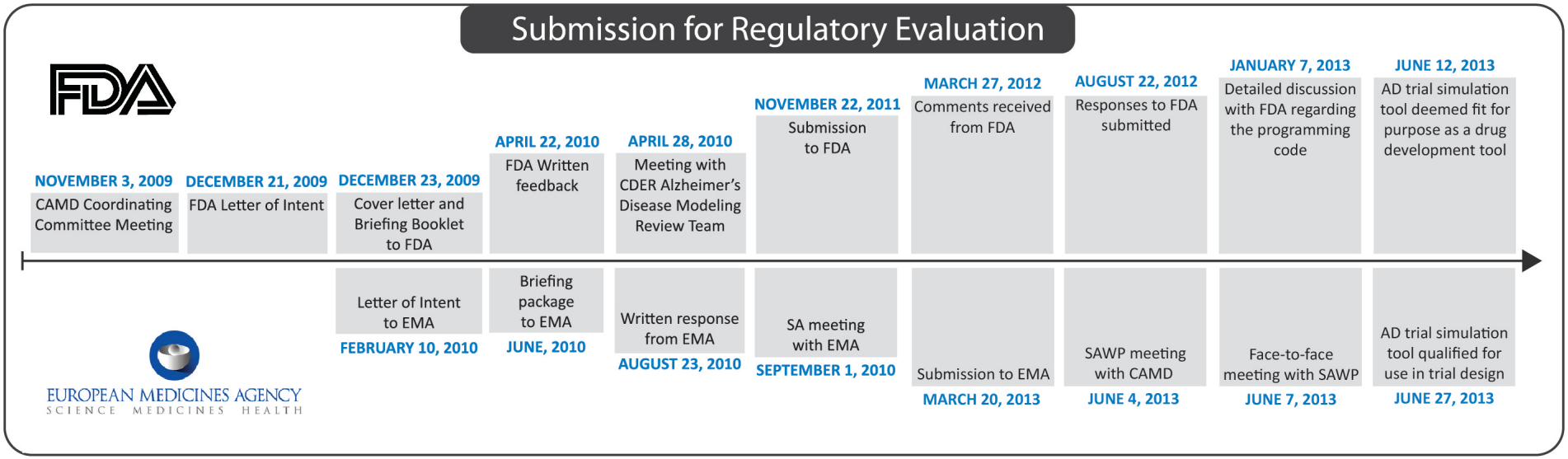
n	639
Age range (yrs)	50-97
Males	280 (44%)
Females	359 (56%)
Follow-up range (days)	479-700
individual follow-up visits	2383



AND THOROUGH INPUT THROUGHOUT THE PROCESS,

AD Drug Disease Trial Model

The regulatory path



EMA qualification opinion posted for public comment:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/07/WC500146179.pdf

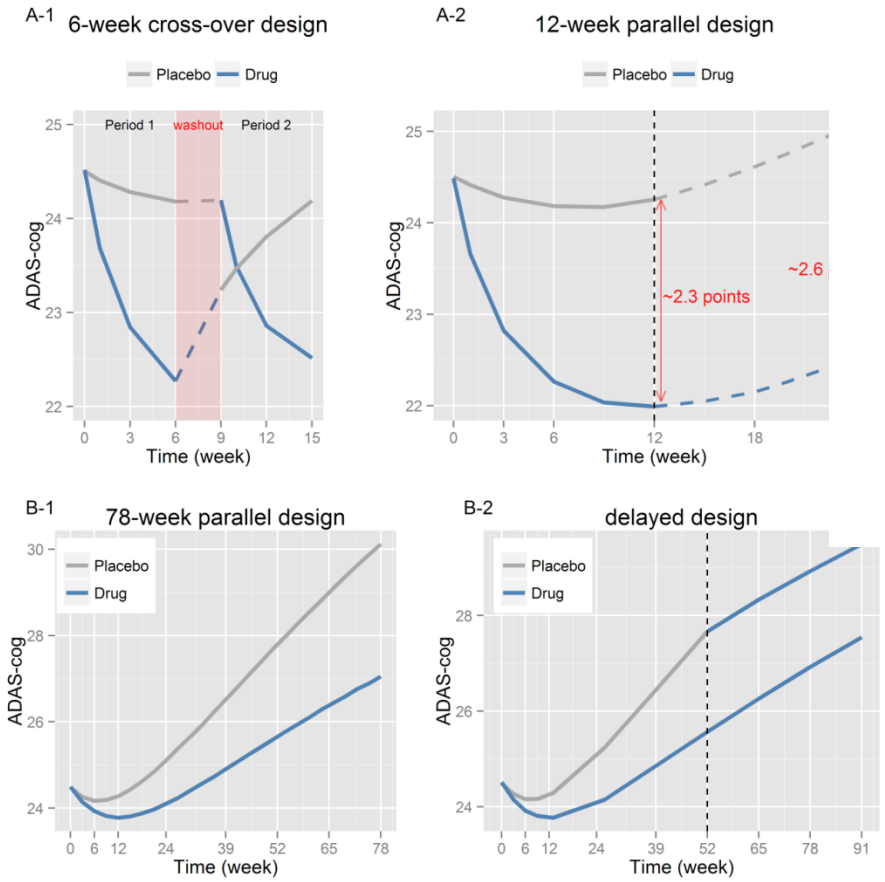
IMPLEMENTED IN A WIDELY AVAILABLE TOOL,

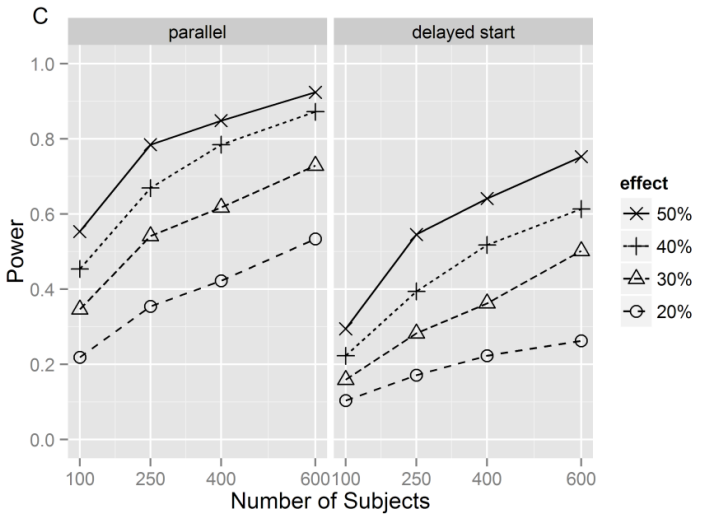
R Simulation Framework

- Patient recruitment acRecruit()
  - Generates patients, their demographics, and disease state
- Patient randomization acRandomize()
  - Assigns patients to treatment arms, time intervals and drug effects (Sx/DM)
- ADAS-cog simulation acRun()
  - Given previous conditions, simulates ADAS-cog scores (may include inter-study variability or dropouts)

WITH CLEAR EXAMPLES OF USE AND APPLICATION,

Simulation Examples





Simulation and Power Calculation for Various Study Designs

Panels A: Simulated 6-week cross-over trials (A-1) versus 12-week parallel trials (A-2) for drugs with only symptomatic effects. Panels B: Simulated 78-week parallel trials (B-1) versus 91-week delayed start trials (B-2) for a disease modifying drugs with 50% decrease on rate of disease progression. Panel C: Power curve of a 78-week parallel study design and a 91-week delayed start design by assumption of different magnitude of disease modifying effect.

LEARNINGS….

Learnings

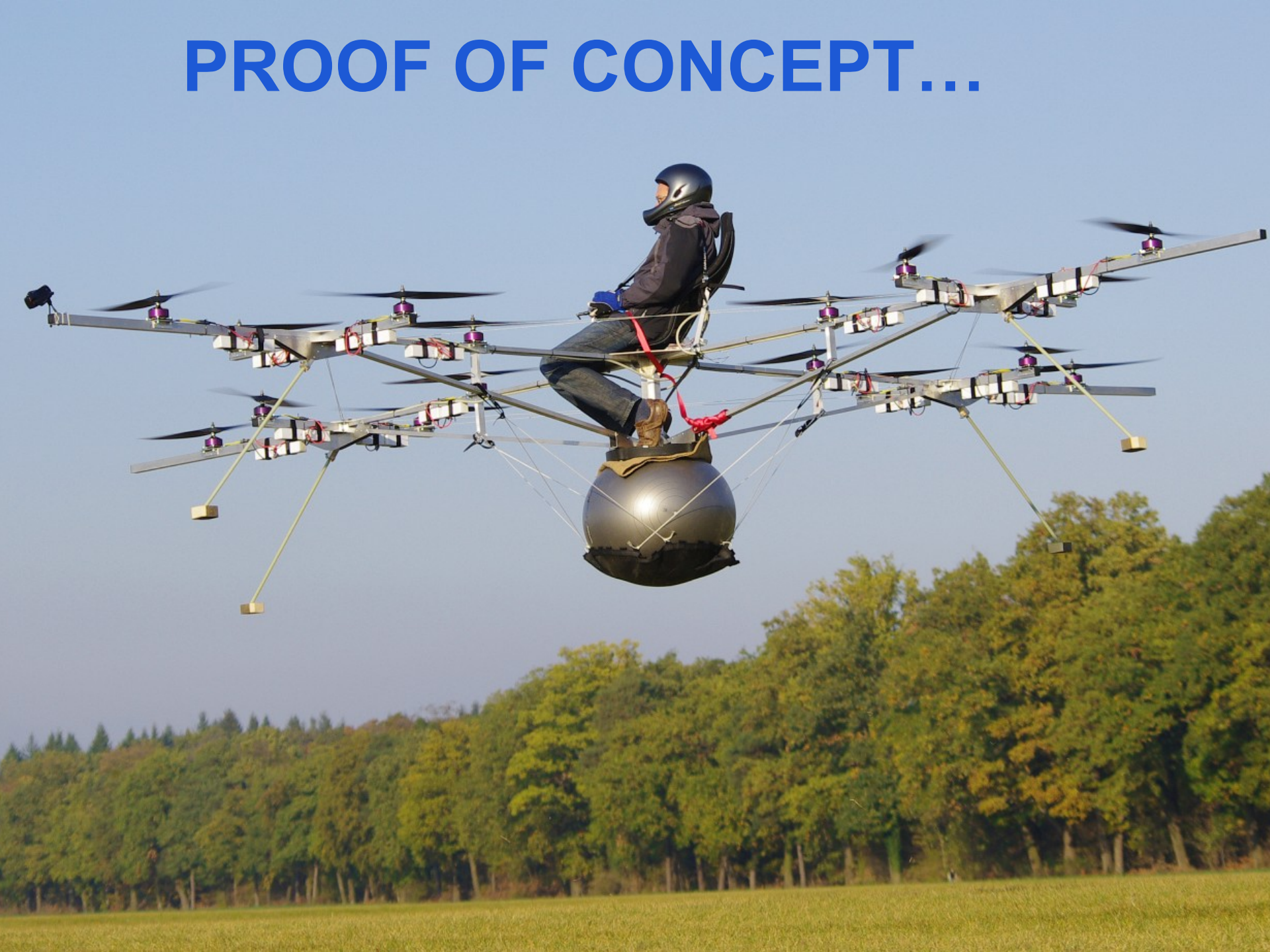
- Use a consortia approach
- Provide clear context of use
- Establish partner relationship with regulators early in process
  - Do not rush to submit a letter of intent, wait until there is clarity in position especially around the “context of use”
- Think about model support, enhancements, support infrastructure, etc
  - Role for organizations such as ISoP
    - User communities

Other Potential Collaboration Activities?

- Systems Pharmacology Models
  - High “energy of activation”
  - Low threshold for upgrade.
- Comparative Effectiveness Models/MBMA
  - Role for organizations such as NICE?

SO WHAT EXACTLY DID YOU ACCOMPLISH?

PROOF OF CONCEPT…



CAMD
CRITICAL PATH INSTITUTE

FROM SMALL BEGINNINGS COME GREAT THINGS

PROVERBS