ACoP8 October 18, 2017

Neighbor's Envy Owner's Pride – Comparator Analysis for Drug Development and Market Access

Post-Approval Decision Making Supported by Modeling and Simulation Based on a Variety of Data Sources

Marc R. Gastonguay, Ph.D. FISoP

METRUM INSTITUTE

METRUM RESEARCH GROUP

Statement of Problem and Context

- Variety of Data Sources

- Post-Approval Decision Making
  - Indirect Comparative Effectiveness
  - Probability of Success in Real World Evidence Trial

- Utility of M&S Given Different Data Sources
  - Limitations
  - Opportunities

A Variety of Data Sources

- Individual-Level Clinical Trial Data
- Individual-Level Patient Registry Data
- Individual-Level Electronic Medical Records
- Summary-Level Literature Meta-Data

Open Access Research

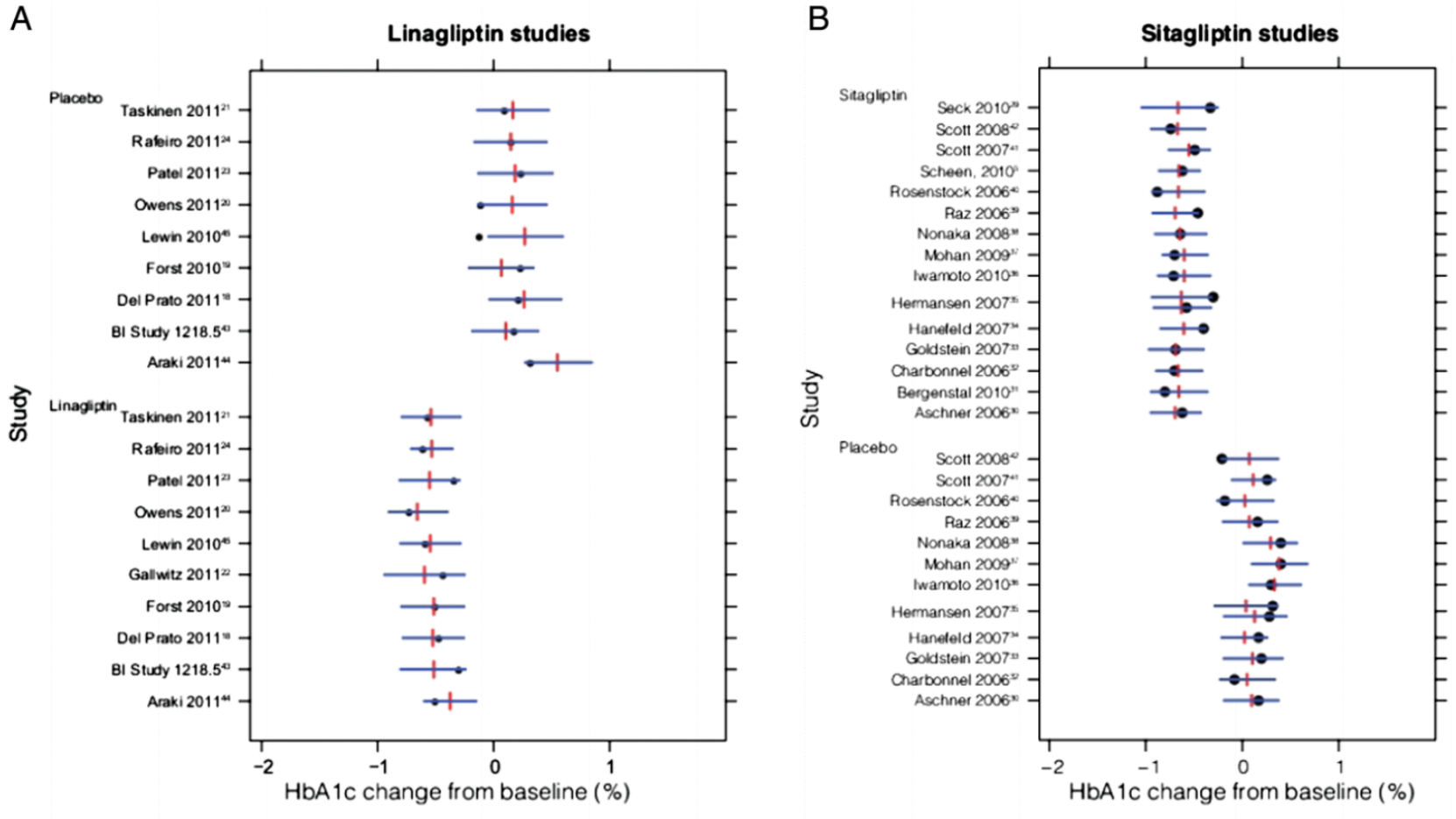
BMJ open
accessible medical research

A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2 diabetes mellitus

Jorge Luiz Gross,[1] James Rogers,[2] Daniel Polhamus,[2] William Gillespie,[2] Christian Friedrich,[3] Yan Gong,[4] Brigitta Ursula Monz,[4] Sanjay Patel,[5] Alexander Staab,[3] Silke Retlich[3]

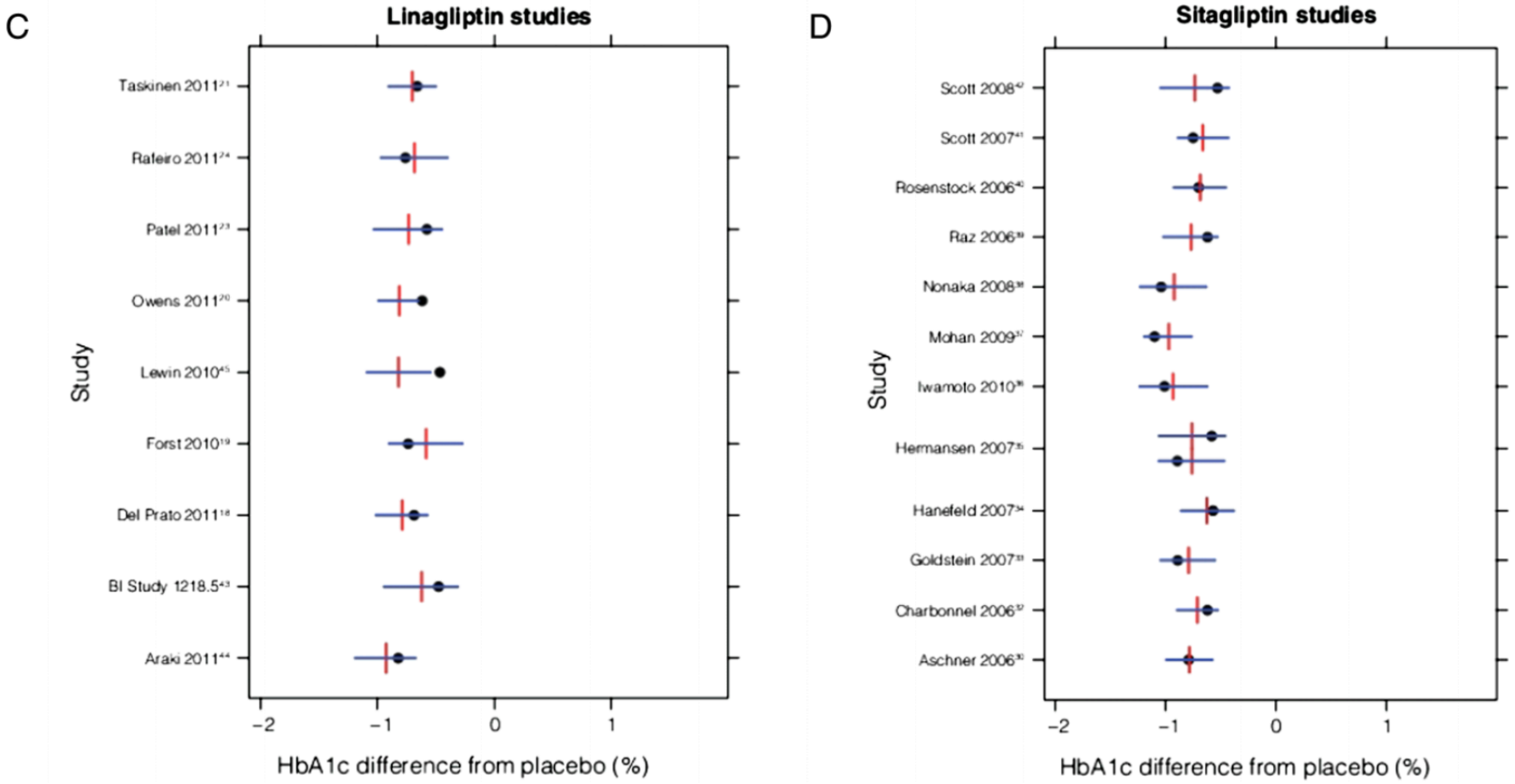
Gross JL, Rogers J, Polhamus D, Gillespie W, Friedrich F, Gong Y, Monz BU, Patel S, Staab A, Retlich S. A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2 diabetes mellitus. BMJ Open 2013, 3:e001844.

Trial Summary Data: HbA1c Change from Baseline



Gross et al BMJ Open 2013, 3:e001844.

Trial Summary Data: HbA1c Difference from Placebo



Gross et al BMJ Open 2013, 3:e001844.

Probability Distribution for Expected Response

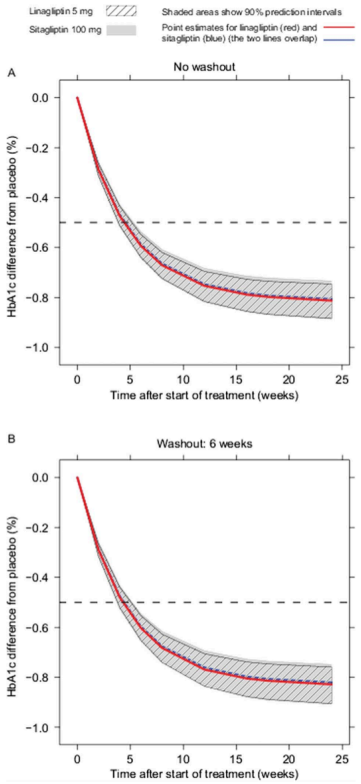


Figure 4 (A) Estimated drug effects on glycated haemoglobin (HbA1c) for reference population, with no pretreatment washout, over 24 weeks (difference from placebo). (B) Estimated drug effects on HbA1c for reference population, with 4-week washout plus 2-week placebo run-in period, over 24 weeks (difference from placebo). Reference population of 1000 participants, baseline HbA1c: 8%, racial composition: 61.5% White, 1.5% Black, 37% Asian.

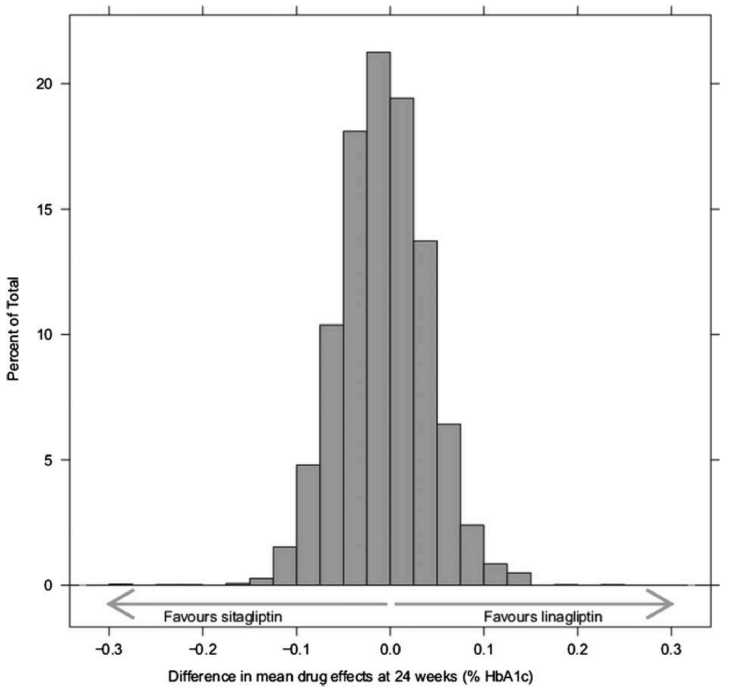
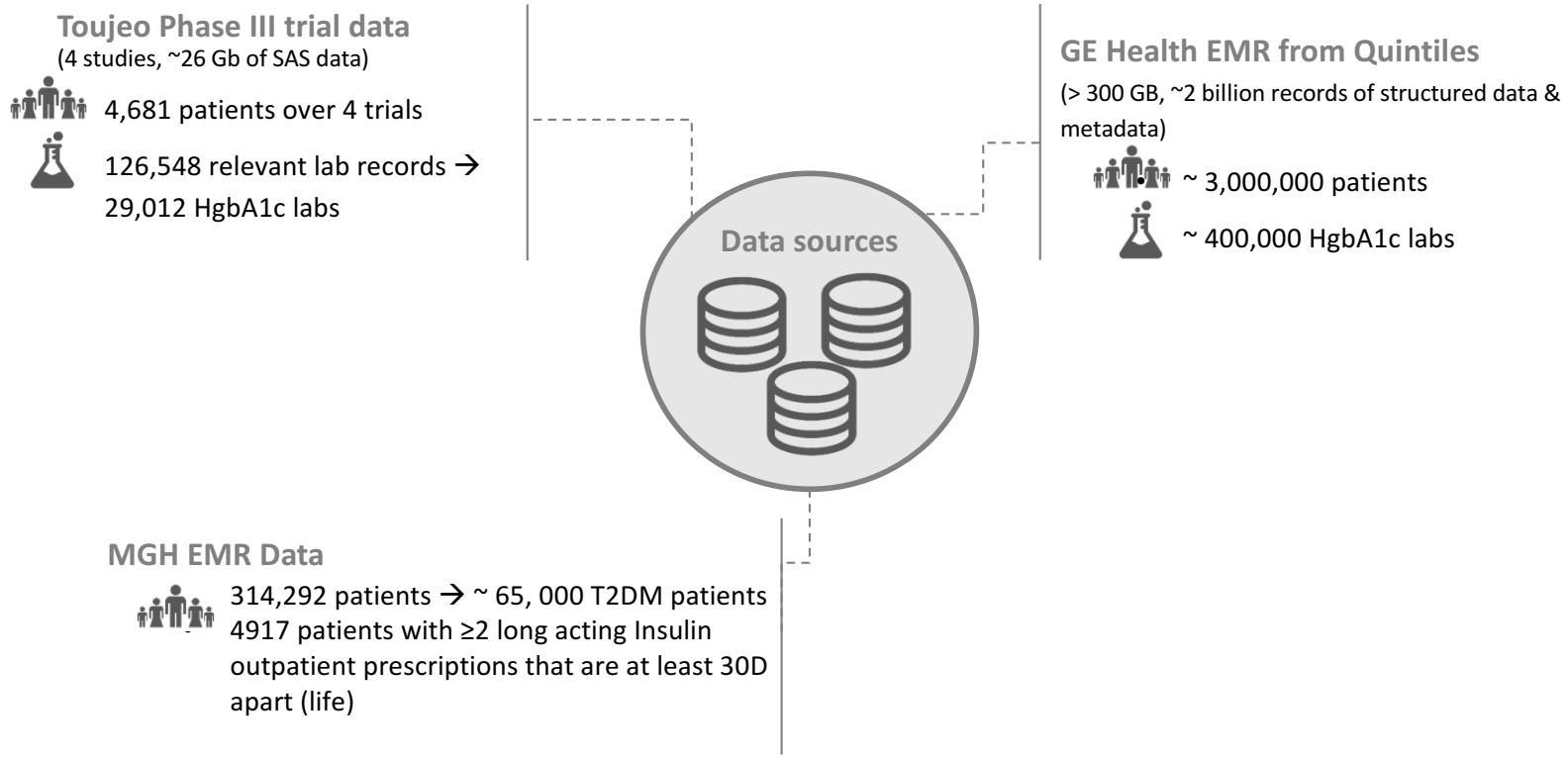


Figure 5 Posterior distribution for the difference in effect estimates between linaglitpin (5 mg) and sitagliptin (100 mg) at 24 weeks. Reference population of 1000 participants (therefore involving 10^6 simulated patients), baseline glycated haemoglobin (HbA1c): 8%, racial composition: 61.5% White, 1.5% Black, 37% Asian.

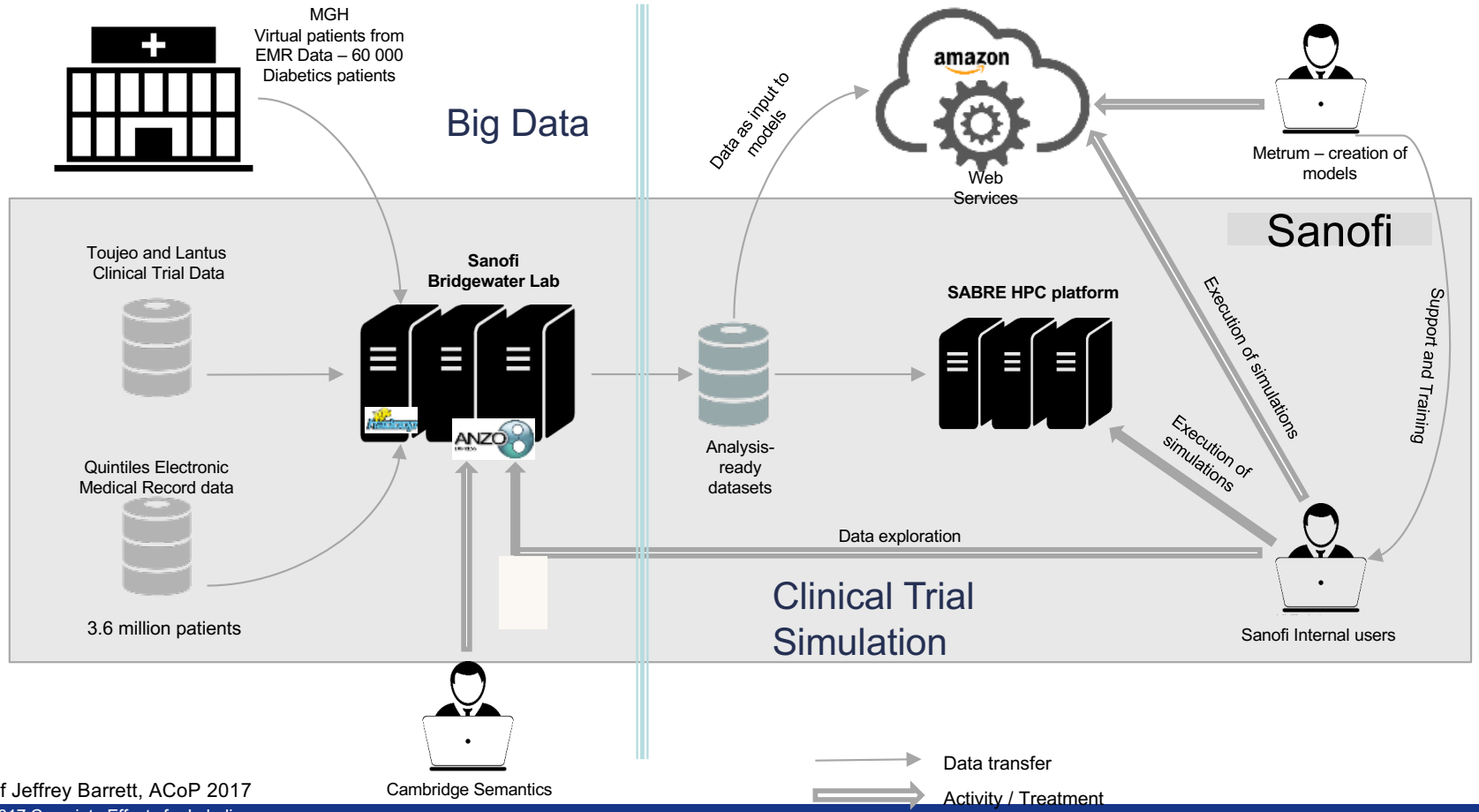
Gross et al BMJ Open 2013, 3:e001844.

Toujeo Real World Evidence Trial Simulation: Data Sources

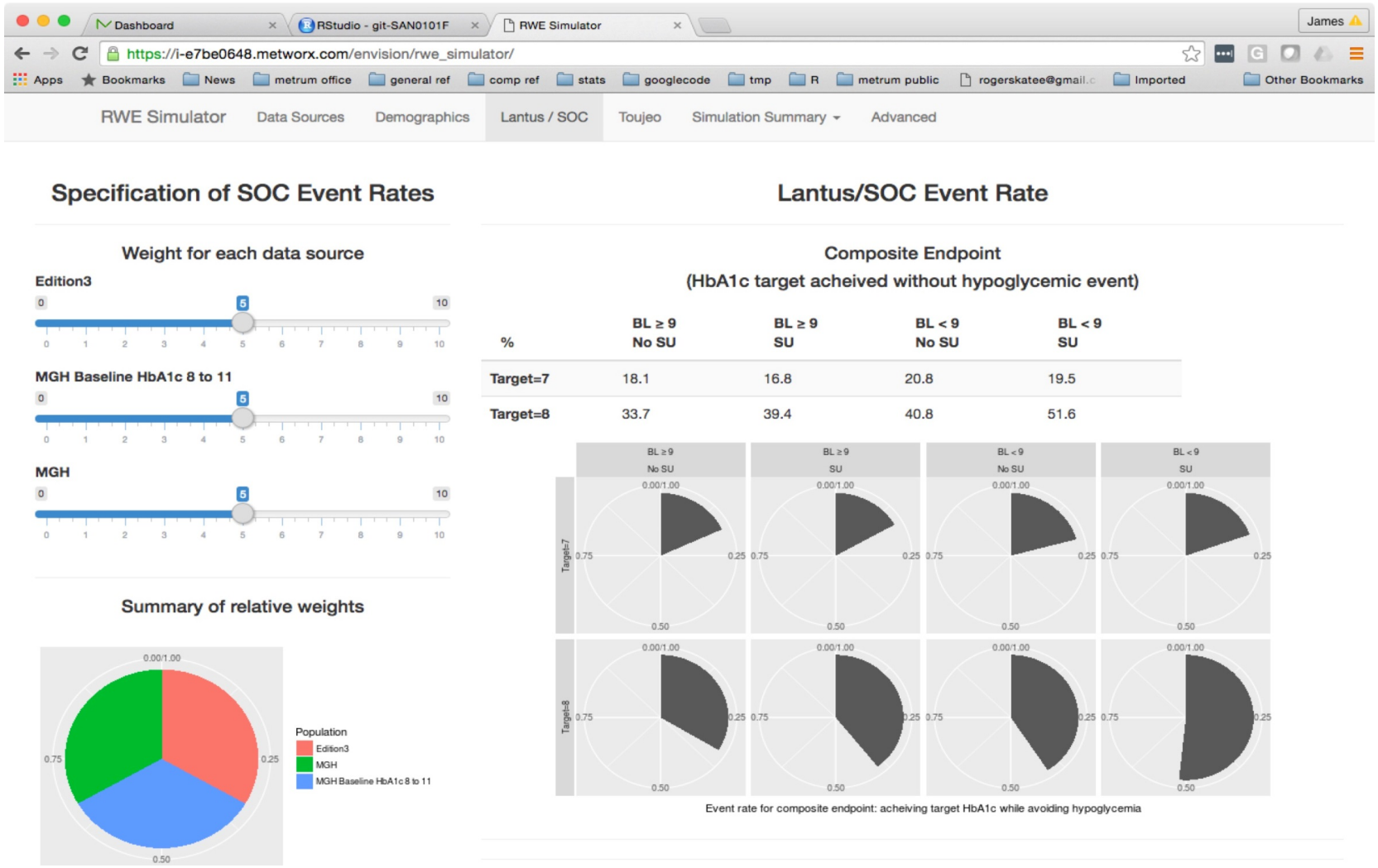


Slide courtesy of Jeffrey Barrett, ACoP 2017

The Big Picture = Systems and Data



Slide courtesy of Jeffrey Barrett, ACoP 2017



Slide courtesy of Jeffrey Barrett, ACoP 2017

Pros/cons of aggregate data (AD) MA

- Pros
  - Relatively easy access to data from public sources
- Cons
  - Not well-suited for inferences about patient-level covariates.
    - Ecological bias/fallacy
    - Aggregate covariate data describes a narrower range of values than individual covariate data
  - For nonlinear models the relationship between the dependent variable and the covariates, e.g., dose or time, is not described by the same function for AD and IPD.
  - Usually no info about correlations among multiple outcomes
  - Model usually not suitable for prediction/simulation of individual outcomes

Slide courtesy of Bill Gillespie, ACoP 2016

Alzheimer's Disease Progression Model

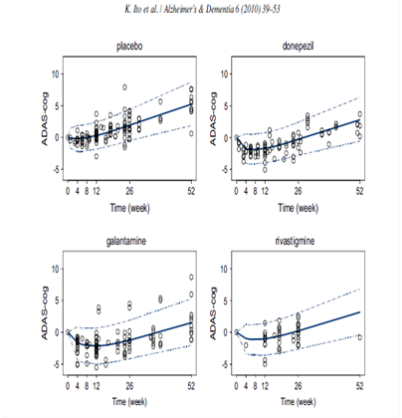
ADNI Defining Alzheimer's Disease

http://www.adni-info.org/

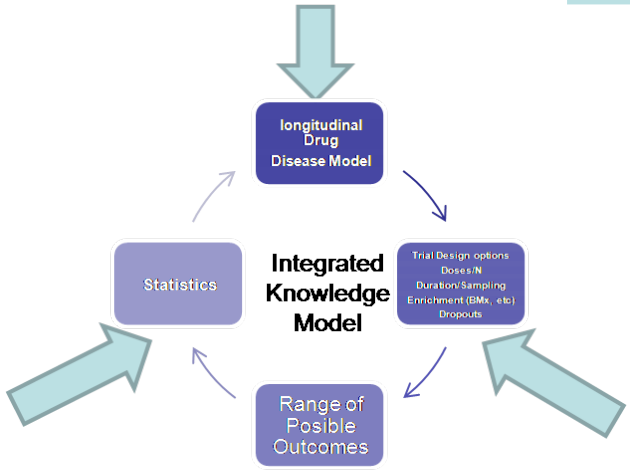
- Natural History
- Interpatient Variability
- Patient Specific Factors
- Imaging and CSF Biomarkers

Sub-populations
Normal (N=200)
MCI (N=400)
Mild AD (N=200)

Literature Meta-Data



- 73 Trials (1990 to Present)
- Interstudy variability
- Estimate of drug treatment effects (magnitude, onset, offset)

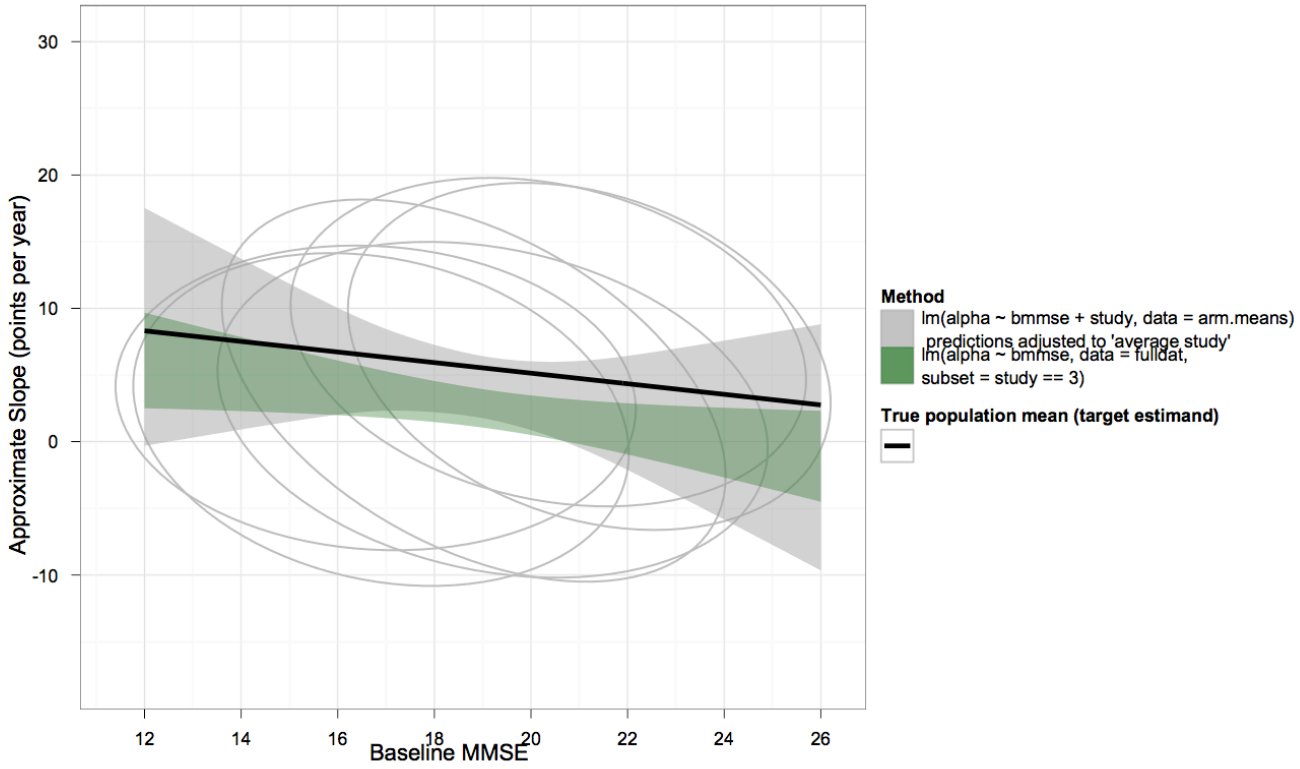


CAMD CRITICAL PATH INSTITUTE

- 9 trials, 3223 patients
- Interpatient Variability
- Patient Specific Factors
- Placebo Effect

http://www.c-path.org/CAMD.cfm

Tradeoffs Between Summary-level Analysis and Patient-level Analysis



Slide courtesy of Jim Rogers, ACoP 2011

J Pharmacokinet Pharmacodyn
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

Objective:

Develop a model to describe the longitudinal progression of ADAS-cog in Alzheimer's disease patients in both natural history and randomized clinical trial settings, utilizing both IPD and AD.

Slide courtesy of Bill Gillespie, ACoP 2016

Hierarchical expectation propagation for Bayesian aggregation of average data*

Sebastian Weber† Andrew Gelman‡ Bob Carpenter ‡ Daniel Lee‡
Michael Betancourt§ Aki Vehtari¶ Amy Racine†

26 Oct 2015

`https://arxiv.org/abs/1602.02055`

- Details methodology for joint analysis of IPD and AD from one study each [17, 18].
- Readily generalized to multiple IPD and AD studies.
- The AD data likelihood is imputed by simulation.
- That is embedded within an overall Bayesian analysis method involving:
  - Analysis of IPD by HMC (Stan),
  - Analysis of AD data by importance sampling, and
  - Iterative updating of both IPD and AD analyses by expectation propagation.

Slide courtesy of Bill Gillesie, ACoP 2016

Why Use Meta-Data at All?

- Comprehensive view of current state of knowledge
- May be only source of estimates for competitor drug effects
- Inferences may be limited to simple treatment mean or SD comparisons
- Combine with individual-level data from other sources

Another Strategy

- Build Models Sequentially by Data Source
  - Model-Based Meta Analysis for Comparator Mean Effect
- Bayesian Data Analysis
  - Informative Prior Distributions for Comparator Mean Effects based on MBMA
  - Individual-Level Data for Disease Progression and Population Variability
  - Individual-Level Data for Proprietary Asset
- Perform Simulation from Bayesian Posterior Distributions

Utility of Different Data Types

	Data Type			
Model-Based Inference or Application	**A. Individual-Level Clinical Trial Data**	**B. Individual-Level Patient Registry Data**	**C. Individual-Level Electronic Medical Records**	**D. Summary-Level Clinical Trial Meta Data (e.g. Mean & SD)**
Treatment Mean Comparison	X		in combination with A or D	X
Treatment SD Comparison	X			X
Individual Covariate Effect Estimation	X			
Covariate Distributions	X	X	X	
Sample Size Calculation	X	in combination with A or D	X	X
Trial Simulation with Individual Inferences or multiple endpoints	X	in combination with A	in combination with A	in combination with A