Applications and Opportunities at the Intersection of Pharmacometrics, Health Economics, Outcomes Research, and Real-World Evidence

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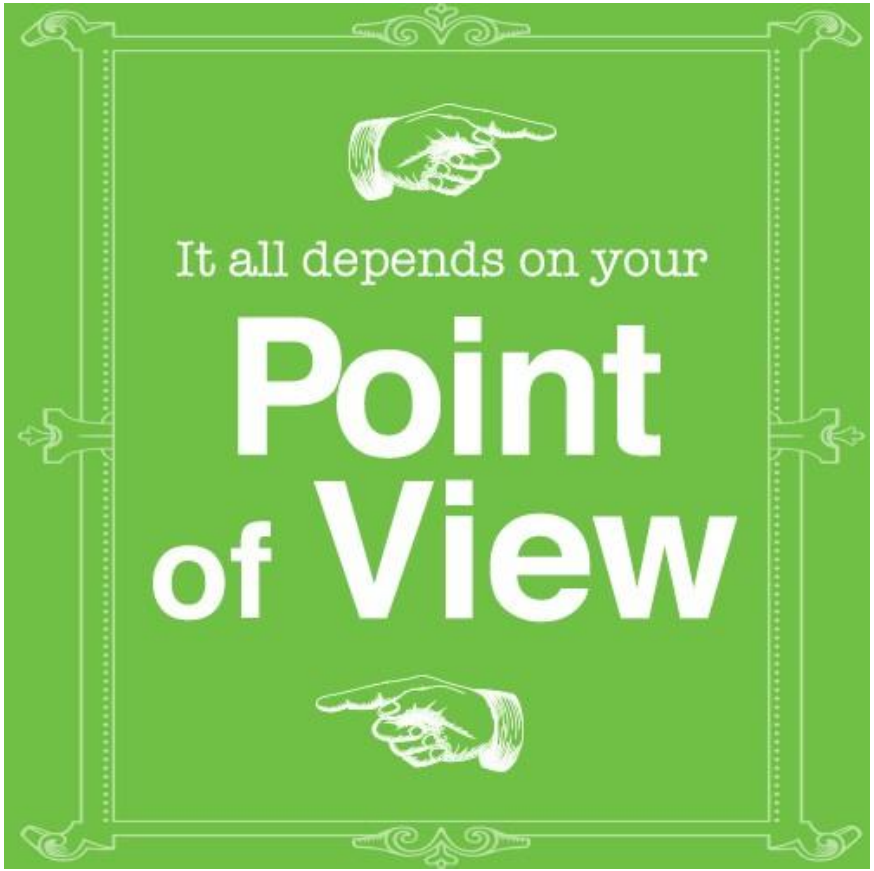
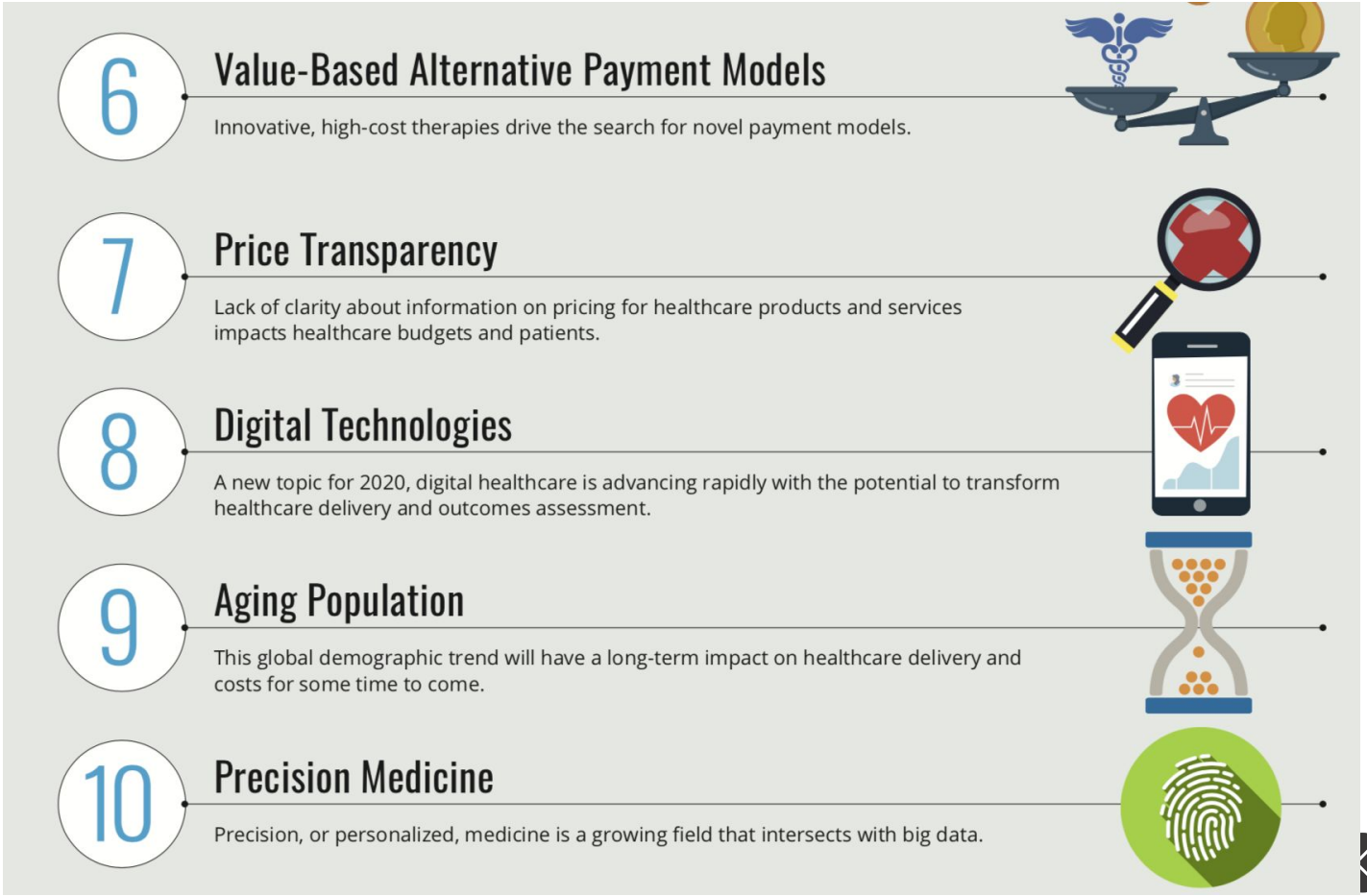
My Perspective as a Pharmacometrician



ISPOR 2020 TOP 10 HEOR TRENDS (1-5)

https://www.ispor.org/top10trends.pdf

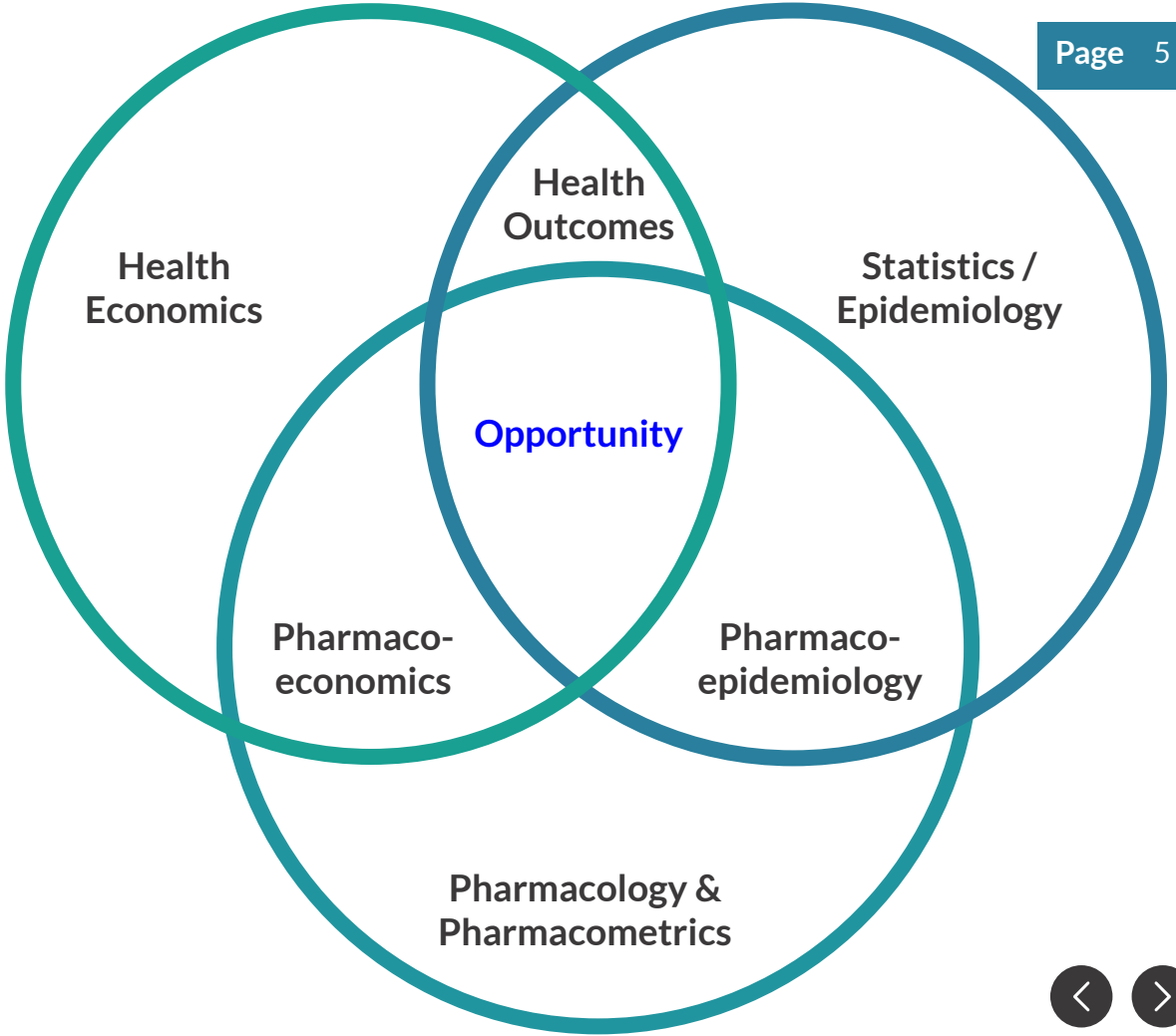
ISPOR 2020 TOP 10 HEOR TRENDS (6-10)



https://www.ispor.org/top10trends.pdf

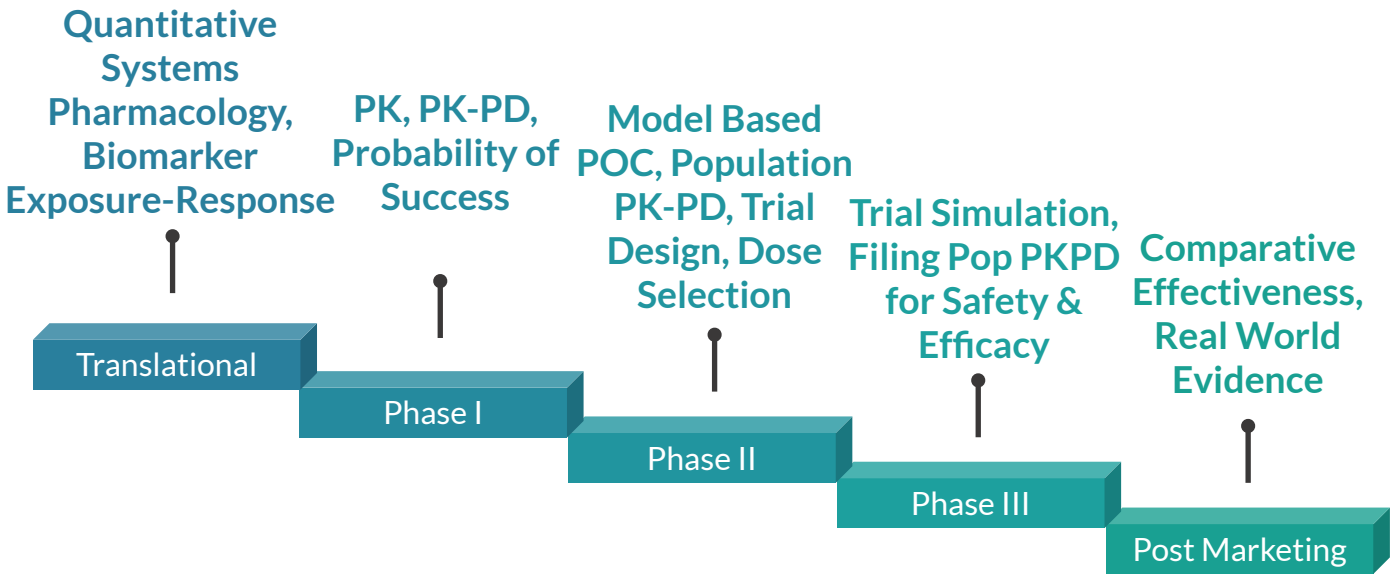
Opportunity
at the Intersection

- Better Inform Drug Development Decisions
- Better Inform Economic and Outcome Decisions



Model-Based Drug Development

Some of the typical methods and activities applied throughout the process



Off-The-Shelf Disease Area Platform Content: Disease Progression, Quantitative Systems Pharmacology, Competitor Model-Based Meta-Analysis, Trial Simulation Tools

Modeling and Simulation Based Decision Making

Start with Key Questions and Potential Decision Paths

- Probability of target product profile
- Treatment regimens
- Trial designs
- Development strategies
- Indications
- Selection of lead candidates

Models

- Drug & disease models
- Treatment population models
- Trial models
- Financial & market models

Other Information Sources

- Public evidence
- Expert opinion / belief

Simulate Outcomes of each Path or Question

Decision Criteria

- Consider cost/benefit trade-offs
  - Safety
  - Clinical utility/efficacy
  - Health Economic
  - Commercial
- Adjusted to consider the value systems of the key stakeholders
  - Patients
  - Health care providers
  - Drug developer
  - Regulators

Assumption Checking

Assess sensitivity of conclusions to uncertainties and assumptions.

Decision

Select highest value path given the current state of knowledge.

Some Examples

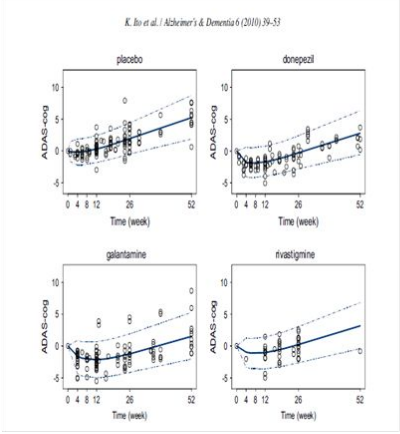
Model-Based POC for Alzheimer's Disease Trial

ADNI Defining Alzheimer's Disease
www.adni-info.org

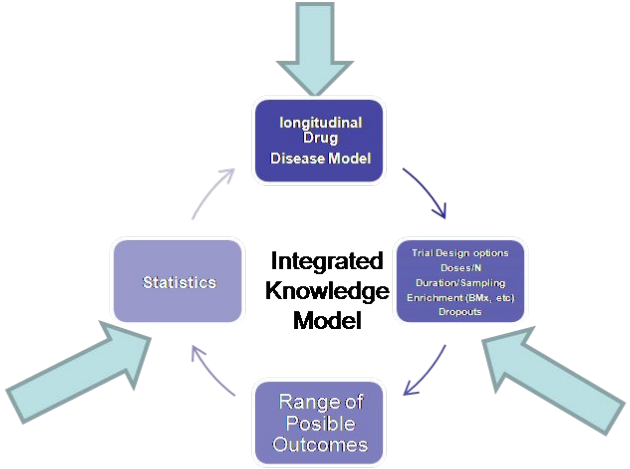
- Natural History
- Interpatient Variability
- Patient Specific Factors
- Imaging and CSF Biomarkers

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
c-path.org/programs/cpad/

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

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

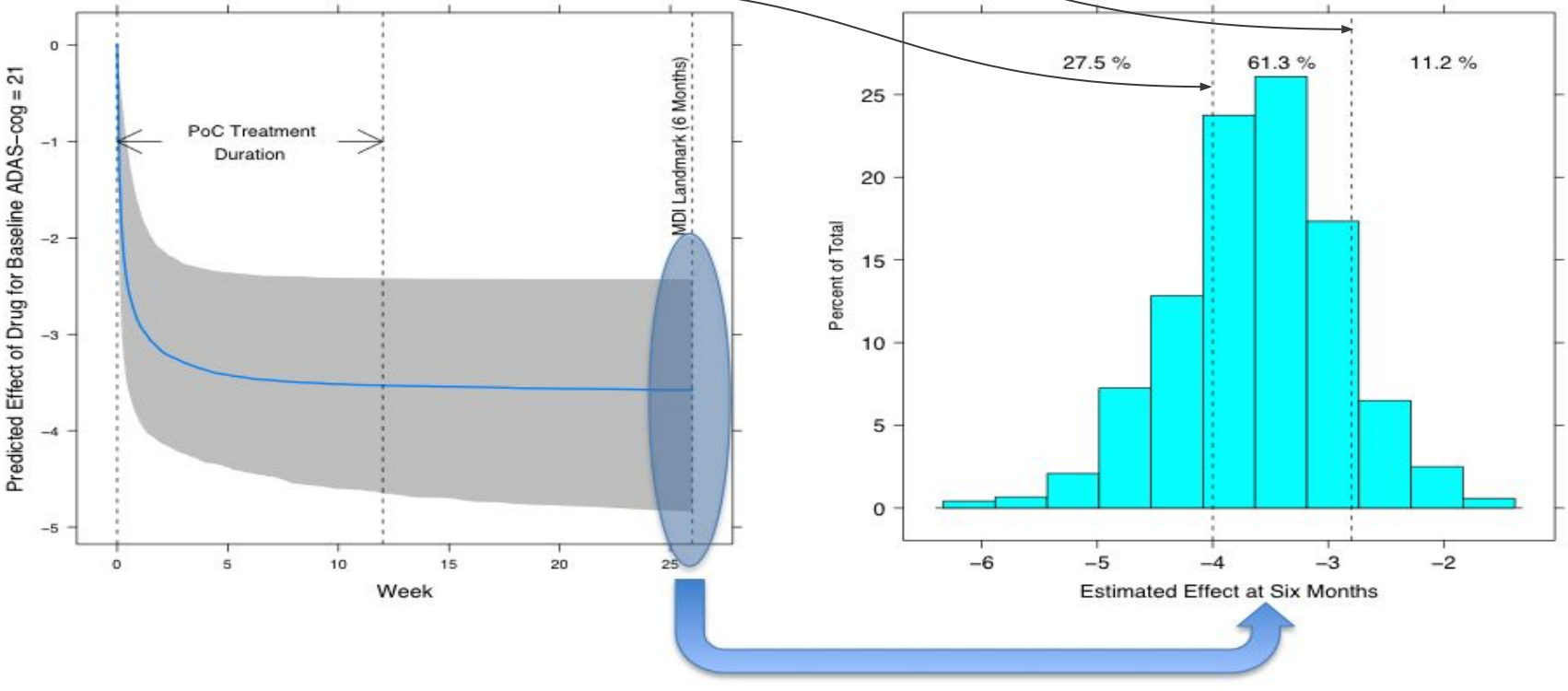
Objective:

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.

Model-Based Projection of TPP for POC Decision

Target product response for change in typical ADAScog score at 6 months:

- must have -2.5 units
- wish for -4 units

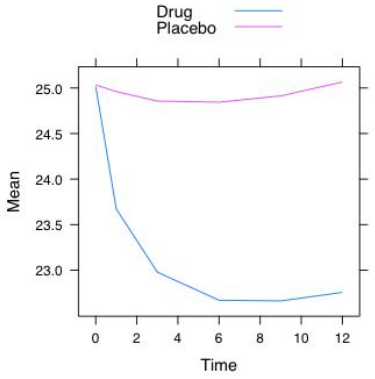


Discussion Points

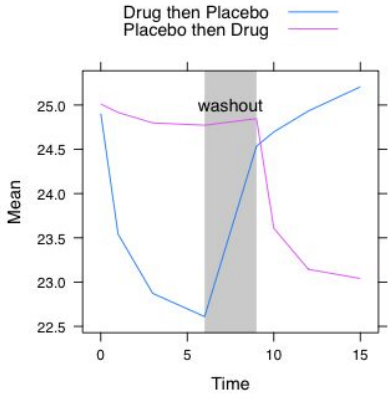
- Are similar disease progression data sets / information sources used in HEOR assessments?

- How else can a quantitative understanding of disease progression be utilized in your decision making?

Exploring POC Trial Design Performance



Given quantitative criteria, explore decision making performance under different assumptions about true drug characteristics.



Assuming drug reaches 50% of maximal effect at 4 weeks:

12 Week Parallel Design

Truth	Decision	
	GO	NO GO
$E(6) = 2$	0%	100%
$E(6) = 4.5$	92%	8%

6 Week Cross-over Design

Truth	Decision	
	GO	NO GO
$E(6) = 2$	10%	90%
$E(6) = 4.5$	92%	8%

$E(6)$ denotes placebo-adjusted drug effect at 6 months;
Table percentages based on 100 simulations

Polhamus D, Rogers J, Gillespie W, French J, and Gastonguay M. From Evidence Synthesis to Trial Optimization: The adsim Package for Model-based Simulation in Alzheimer's Disease PAGE 21 June 2012 (http://metrumrg.com/assets/pubs/page_2012_polhamus.pdf)

Indirect Comparative Efficacy

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]

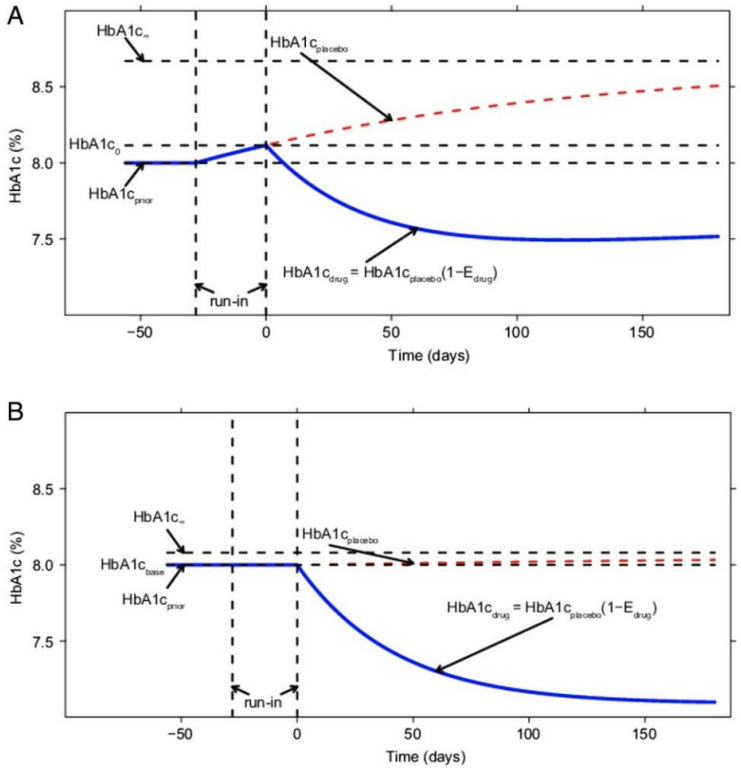
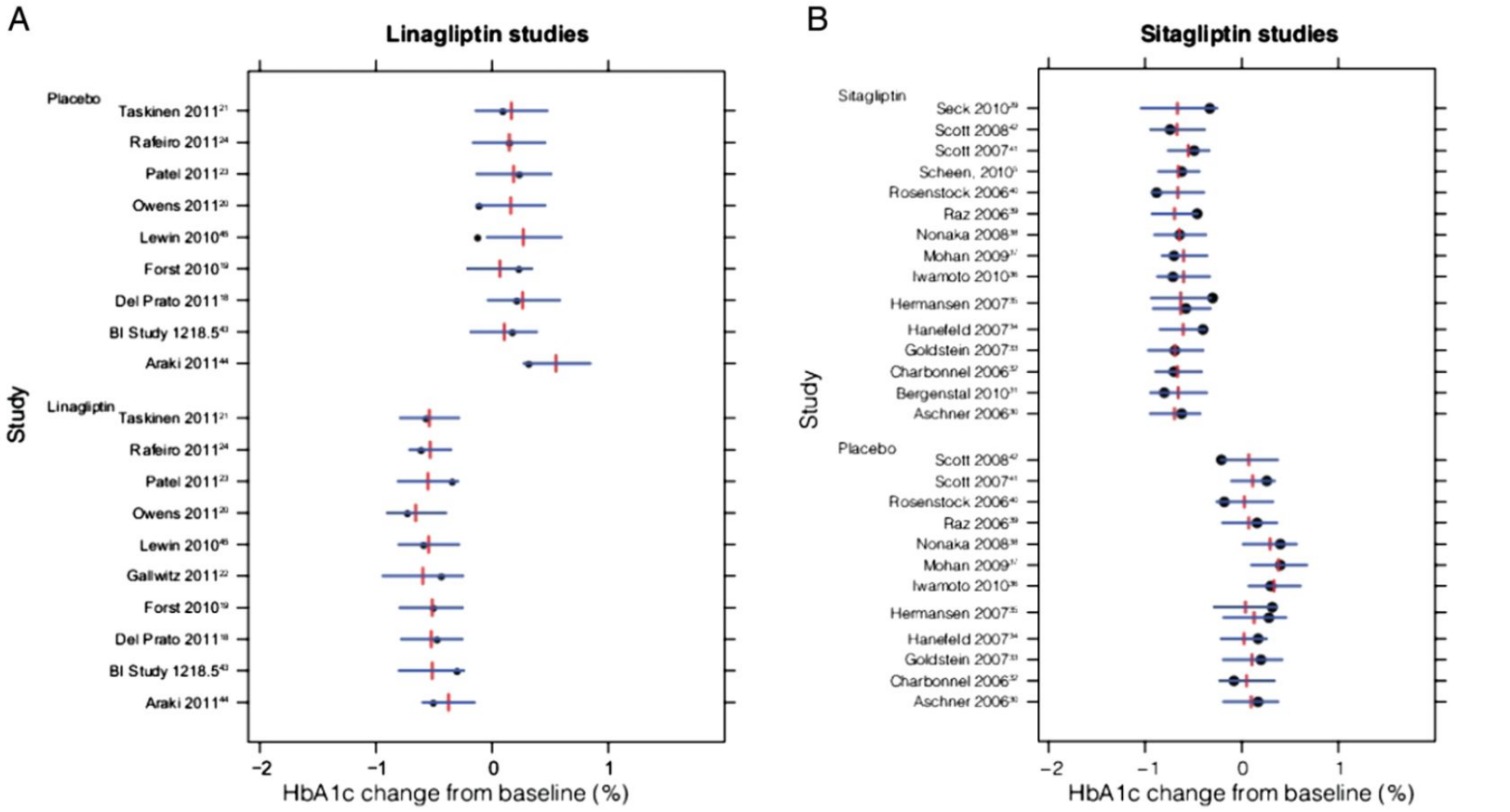


Figure 1 (A) Graphic representation of the components of the final model, for study arms that included patients washing out their prior antihyperglycaemic medication in the run-in period. (B) Graphic representation of the components of the final model, for study arms that included patients who were treatment-naïve or had completely washed out their prior antihyperglycaemic medication before enrolment.

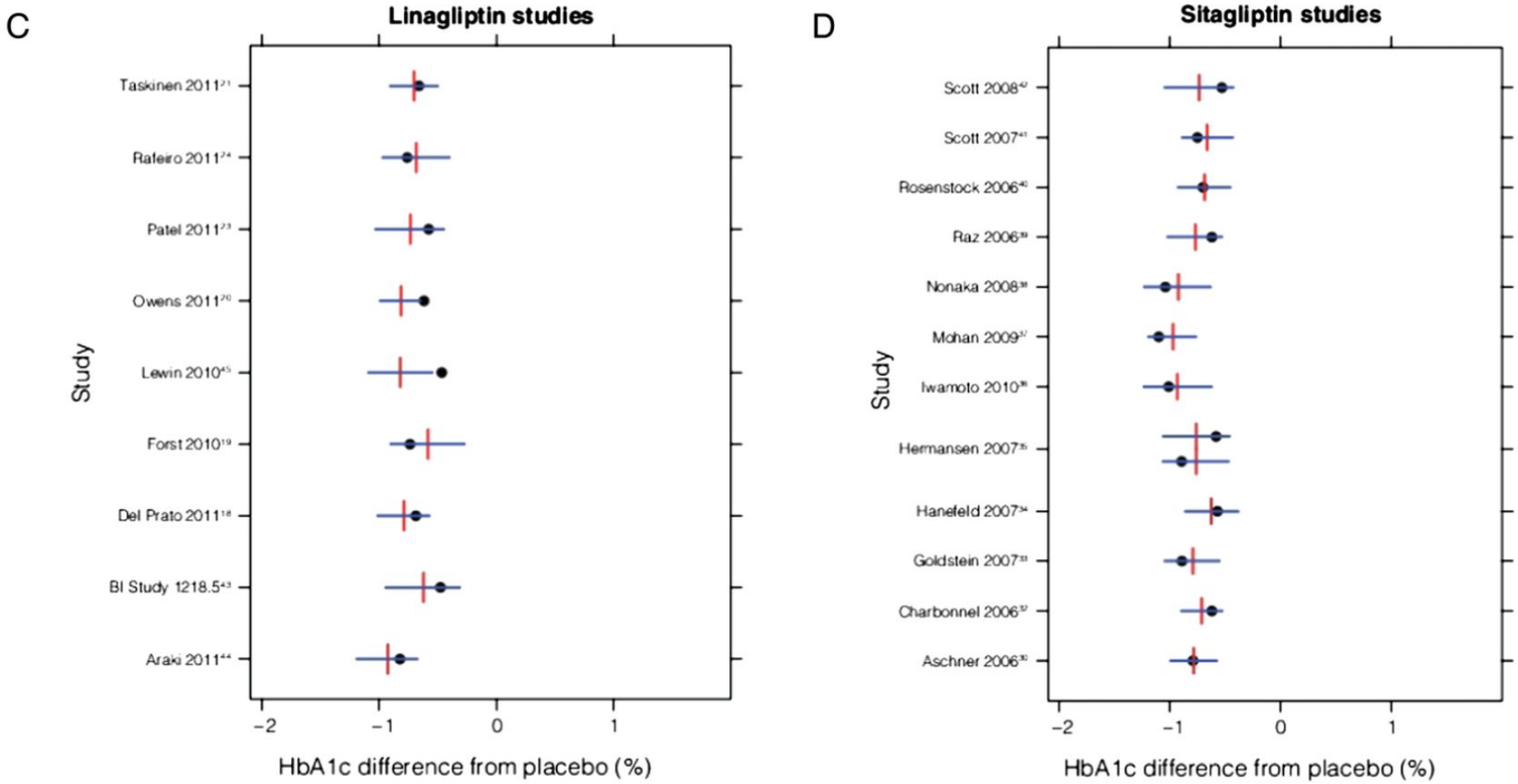
Gross JL, Rogers J, Polhamus D, Gillespie W, Friedrich F, Gong Y, Monz BU, Patel S, Staab A, Retlich S. A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2 diabetes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

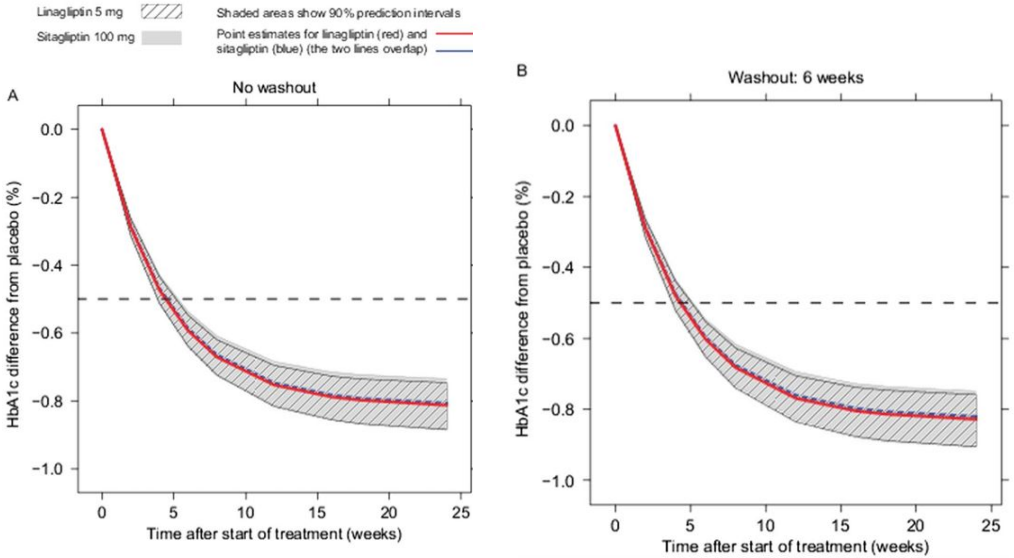


Figure 4 (A) Estimated drug effects on glycated haemoglobin (HbA1c) for reference population, with no pretreatment washout, over 24 weeks (difference from placebo). (B) Estimated drug effects on HbA1c for reference population, with 4-week washout plus 2-week placebo run-in period, over 24 weeks (difference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

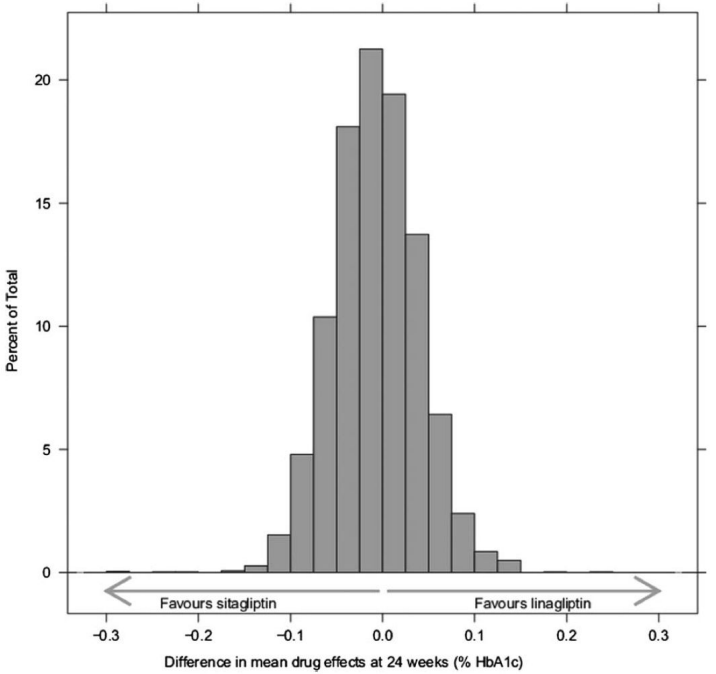


Figure 5 Posterior distribution for the difference in effect estimates between linaglitpin (5 mg) and sitagliptin (100 mg) at 24 weeks. Reference population of 1000 participants (therefore involving 10^6 simulated patients), baseline glycated haemoglobin (HbA1c): 8%, racial composition: 61.5% White,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

Gross et al BMJ Open 2013, 3:e001844.

Impact on Health Technology Assessment

Advice

following a full submission:

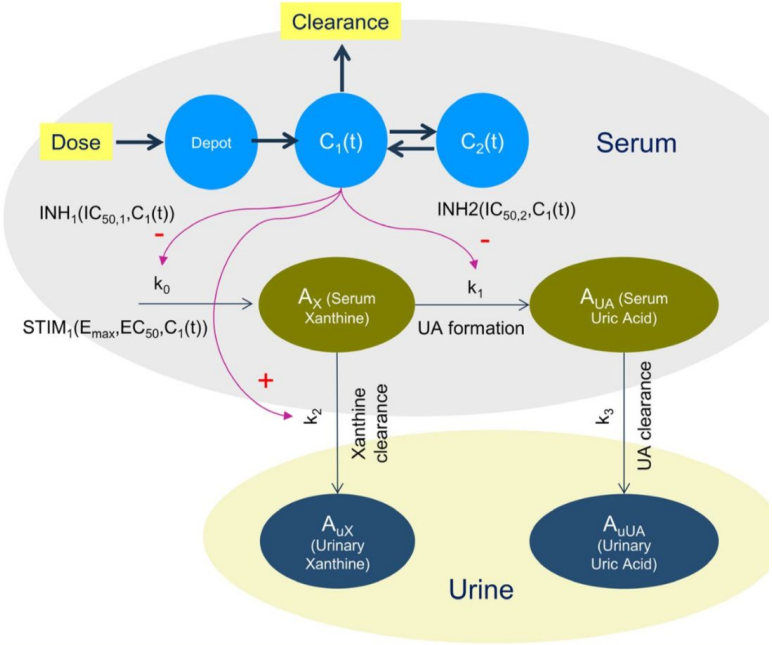
linagliptin (Trajenta®) is accepted for restricted use within NHS Scotland.

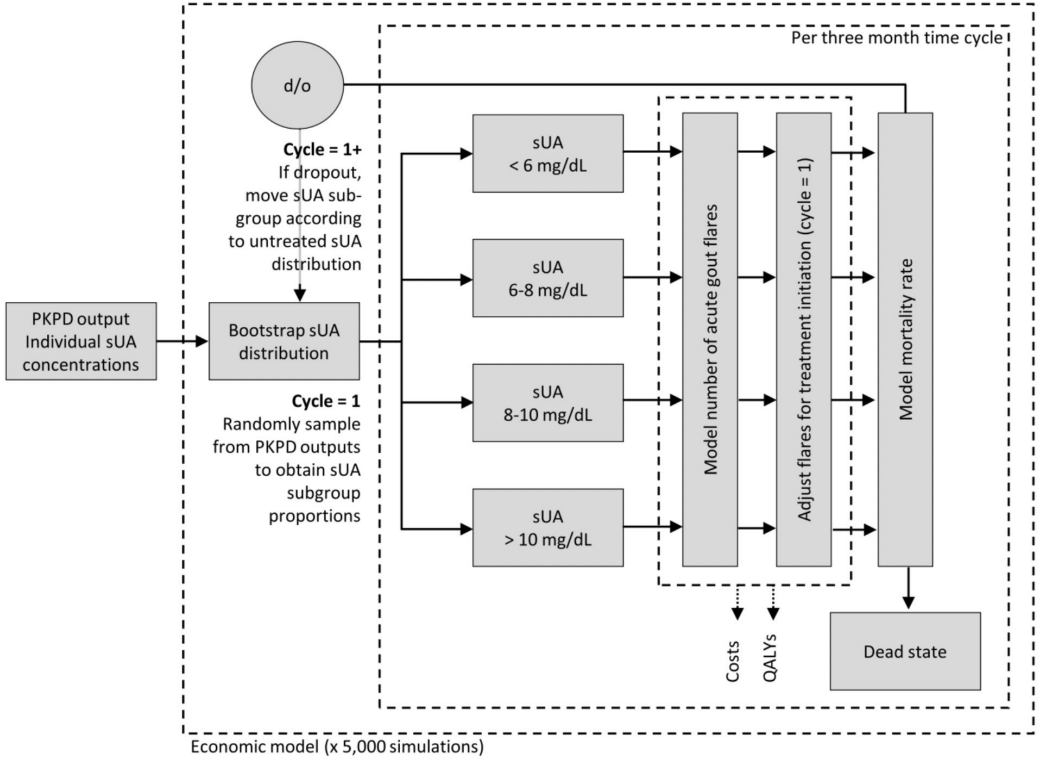
Indication under review: the treatment of type 2 diabetes mellitus to improve glycaemic control in adults:

https://www.scottishmedicines.org.uk/medicines-advice/linagliptin-trajenta-fullsubmission-85013/

Linking PMX and PE: Xanthine Oxidase Inh. & Gout

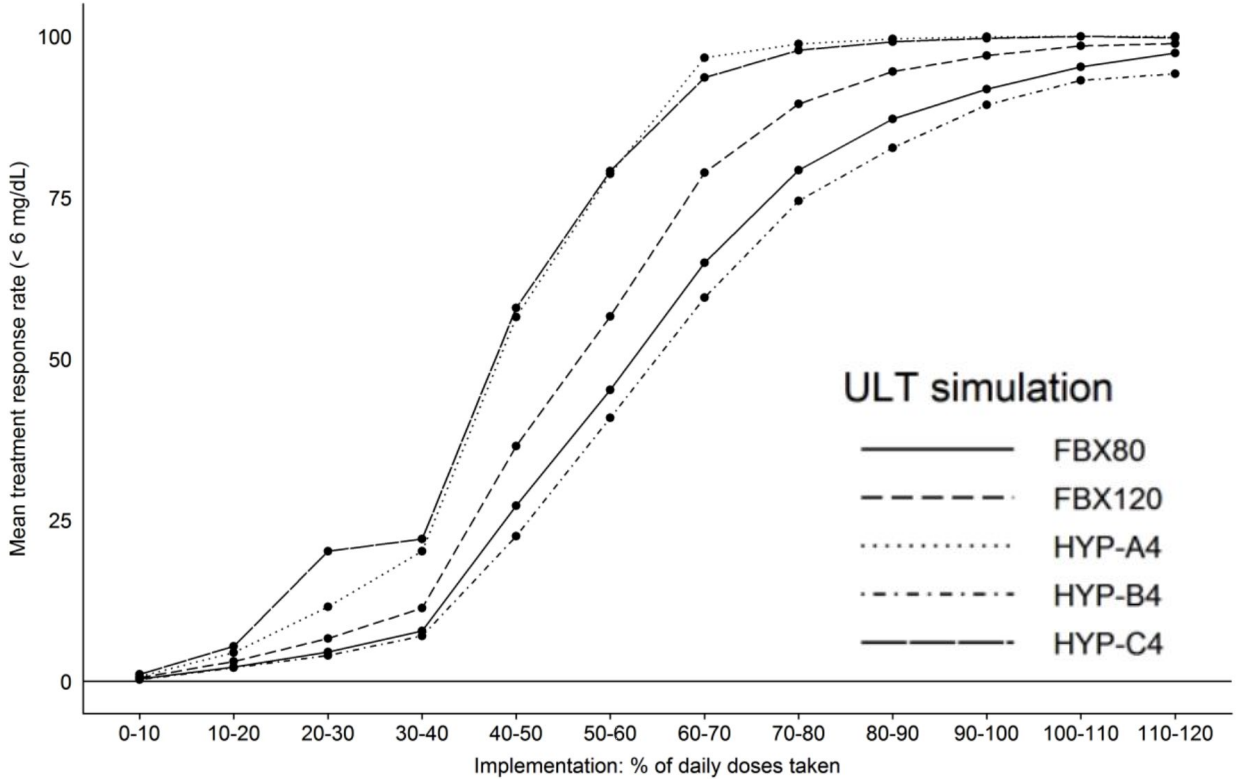
Individual-Level PKPD Modeling and Simulation





Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout. Daniel Hill-McManus;Scott Marshall;Elena Soto;Dyfrig A Hughes ISSN: 0009-9236 , 1532-6535; DOI: 10.1002/cpt.1454. Clinical pharmacology & therapeutics : CPT. , 2019, Vol.106(3), p.652-660

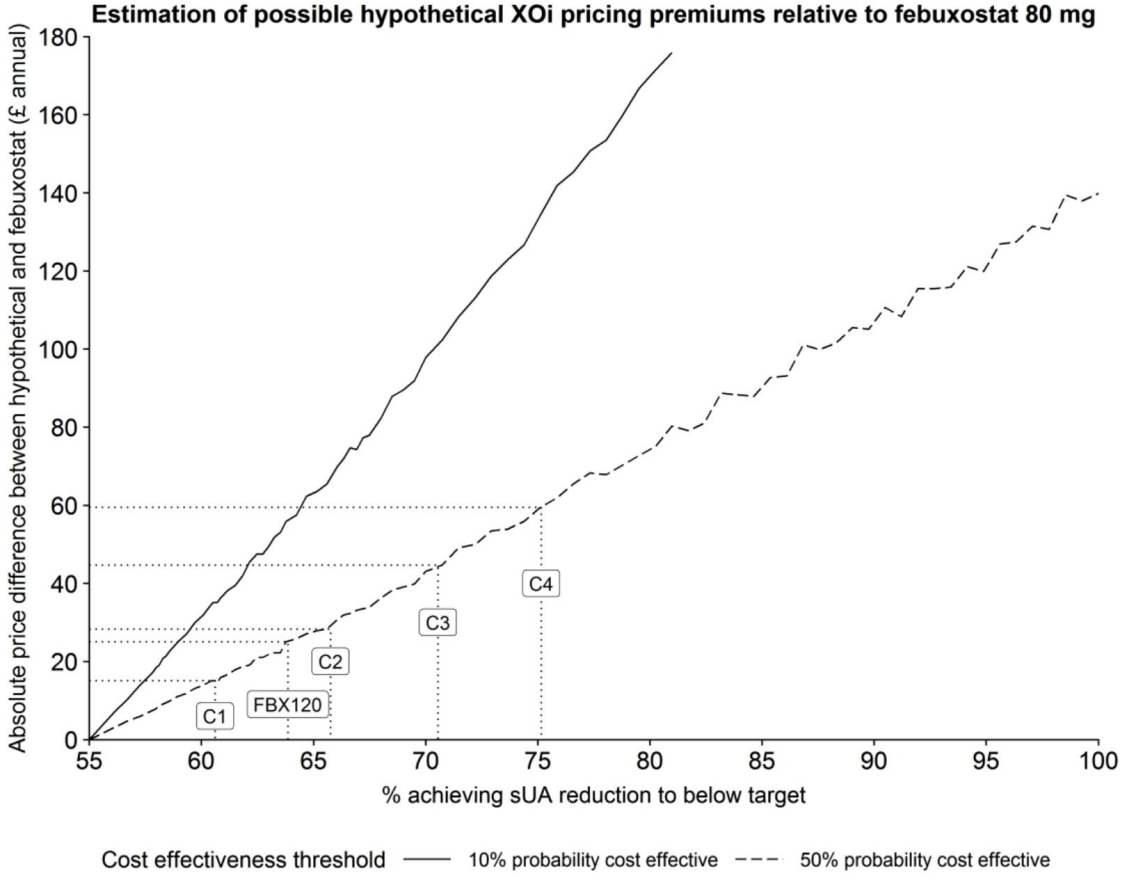
Simulation: Response vs. Adherence



- Simulation-based comparison of febuxostat and hypothetical analogues
- Varied clearance, potency, for analogues
- Informed by adherence RWE

Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout. Daniel Hill-McManus;Scott Marshall;Elena Soto;Dyfrig A Hughes ISSN: 0009-9236 , 1532-6535; DOI: 10.1002/cpt.1454. Clinical pharmacology & therapeutics : CPT. , 2019, Vol.106(3), p.652-660

Simulation: Pricing vs Response



Curve of estimated pricing to achieve cost effectiveness versus febuxostat 80 mg with probability of 50% and 10% at a willingness to pay threshold of £20,000 per QALY

Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout. Daniel Hill-McManus;Scott Marshall;Elena Soto;Dyfrig A Hughes ISSN: 0009-9236 , 1532-6535; DOI: 10.1002/cpt.1454. Clinical pharmacology & therapeutics : CPT. , 2019, Vol.106(3), p.652-660

Discussion Points

- How can a projection of expected pricing premium impact early drug development decision making?

- In addition to strategies aimed at modifying the impact of non-adherence, what other strategies are of interest from an economic/outcomes point of view?

Denosumab Pharmacoeconomic Analysis

JOURNAL OF MEDICAL ECONOMICS, 2018
VOL. 21, NO. 5, 525–536
https://doi.org/10.1080/13696998.2018.1445634
Article 0212-FT.R1/1445634

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

A cost-effectiveness analysis of denosumab for the prevention of skeletal-related events in patients with multiple myeloma in the United States of America

Noopur Raje[a], Garson David Roodman[b], Wolfgang Willenbacher[c], Kazuyuki Shimizu[d], Ramón García-Sanz[e], Evangelos Terpos[f], Lisa Kennedy[g], Lorenzo Sabatelli[h], Michele Intorcia[h] and Guy Hechmati[i]

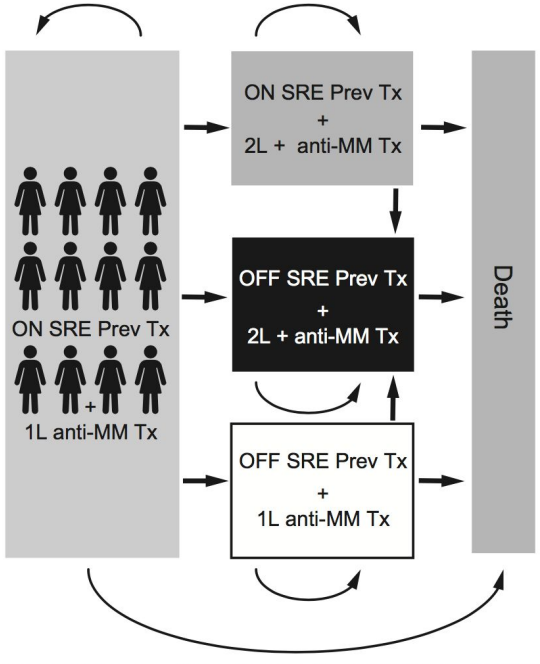


Figure 1. Depiction of model health states. 1L, first line; 2L+, second line or later; Abbreviations. MM, multiple myeloma; OFF SRE Prev Tx, patients not receiving treatment to prevent SREs; ON SRE Prev Tx, patients receiving treatment to prevent SREs; SRE, skeletal-related event; Tx, treatment.

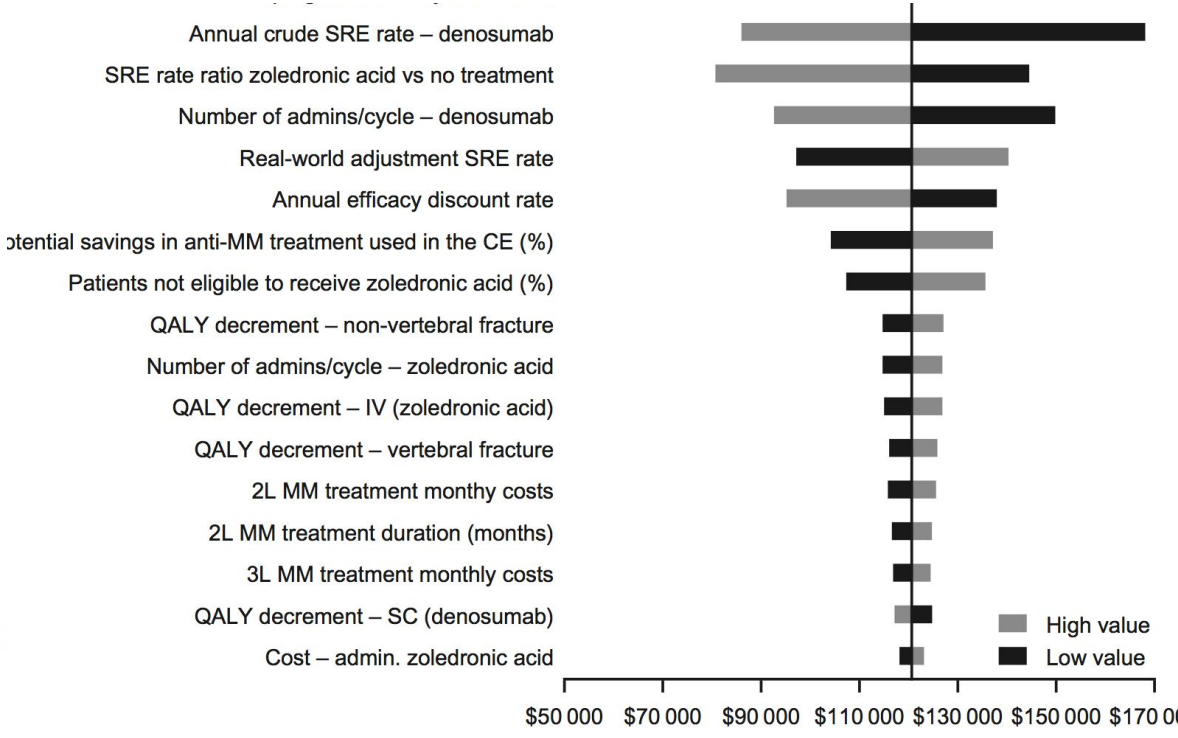
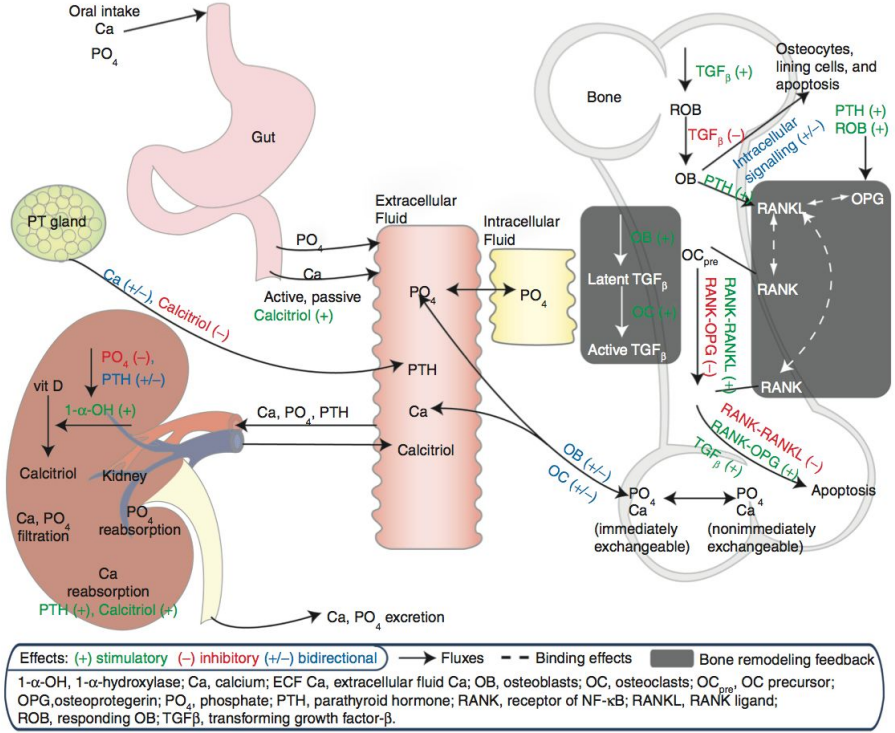


Figure 4. One-way deterministic sensitivity analyses of key variables from (a) the societal perspective and (b) the payer perspective. Ranges for para were as follows: annual efficacy discount rate = 0.00–0.05; percentage of patients not eligible to receive zoledronic acid = 0.05–0.15; annual crude denosumab = 0.55–0.64; annual crude SRE rate of zoledronic acid = 0.58–0.67; real world adjustment SRE rate = 2.01–4.01; SRE rate ratio for zoledron treatment = 0.42–0.82; zoledronic acid cost of administration = 189–231; denosumab number of cycles = 0.79–0.97; zoledronic acid number of cycles post-progression utility decrement = 0.57–0.72; QALY decrement SC = 0.0009–0.0014; QALY decrement IV = 0.0017–0.0025; QALY decrement verte =0.05–0.15; QALY decrement non-vertebral fracture = 0.05–0.15; MM second-line treatment duration = 7.66–9.36; percentage of potential savings in a ment used in the cost-effectiveness analysis = 0.40–0.60; second-line MM treatment monthly costs = 16,430–20,081; third-line MM treatment m s = 16,530–20,204. Abbreviations. 2L, second line; 3L, third line; CE, cost-effectiveness analysis; IV, intravenous; MM, multiple myeloma; RR, ri subcutaneous injection; SRE, skeletal-related event; QALY, quality-adjusted life-year.

Multi-Scale Systems Pharmacology Models



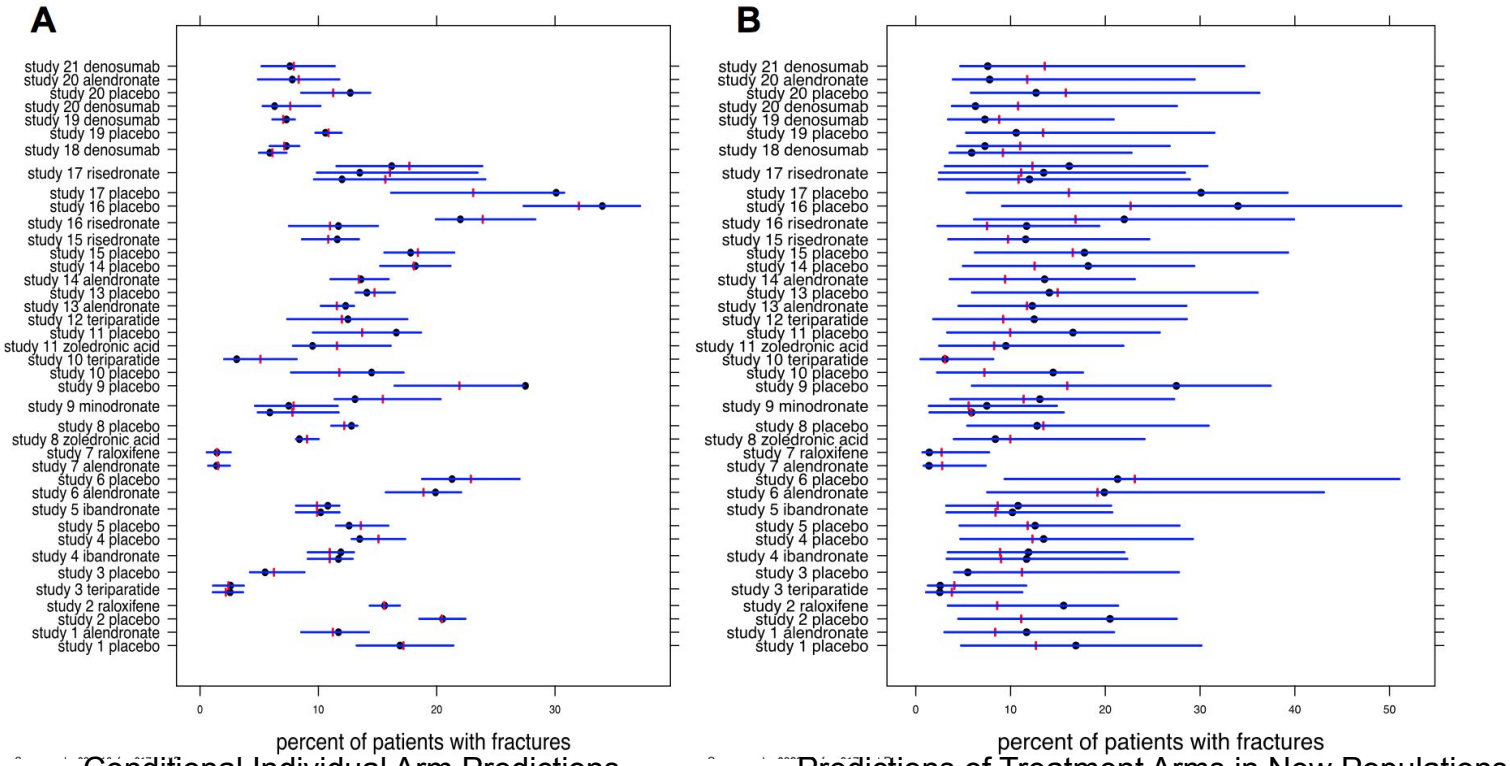
Peterson, MC and Riggs, MM. Predicting Nonlinear Changes in Bone Mineral Density Over Time Using a Multiscale Systems Pharmacology Model CPT: Pharmacomet. Syst. Pharmacol. November 2012

- Osteoporosis
- Primary Hyperparathyroidism
- Hyperparathyroidism Secondary to Chronic Kidney Disease

- Estrogen Modulators
- Bisphosphonates
- Parathyroid Hormone
- RANK-L pathway
- Wnt Signaling

- Bone Biomarkers
- Bone Mineral Density
- Fracture

Fracture Rate MSSP/Model-Based Meta Analysis



Conditional Individual Arm Predictions

Predictions of Treatment Arms in New Populations

RJ Eudy-Byrne, W Gillespie, MM Riggs, MR Gastonguay. A model of fracture risk used to examine the link between bone mineral density and the impact of different therapeutic mechanisms on fracture outcomes in patients with osteoporosis J Pharmacokinet Pharmacodyn (2017) 44:599–609

Fracture Hazard Ratio by Treatment

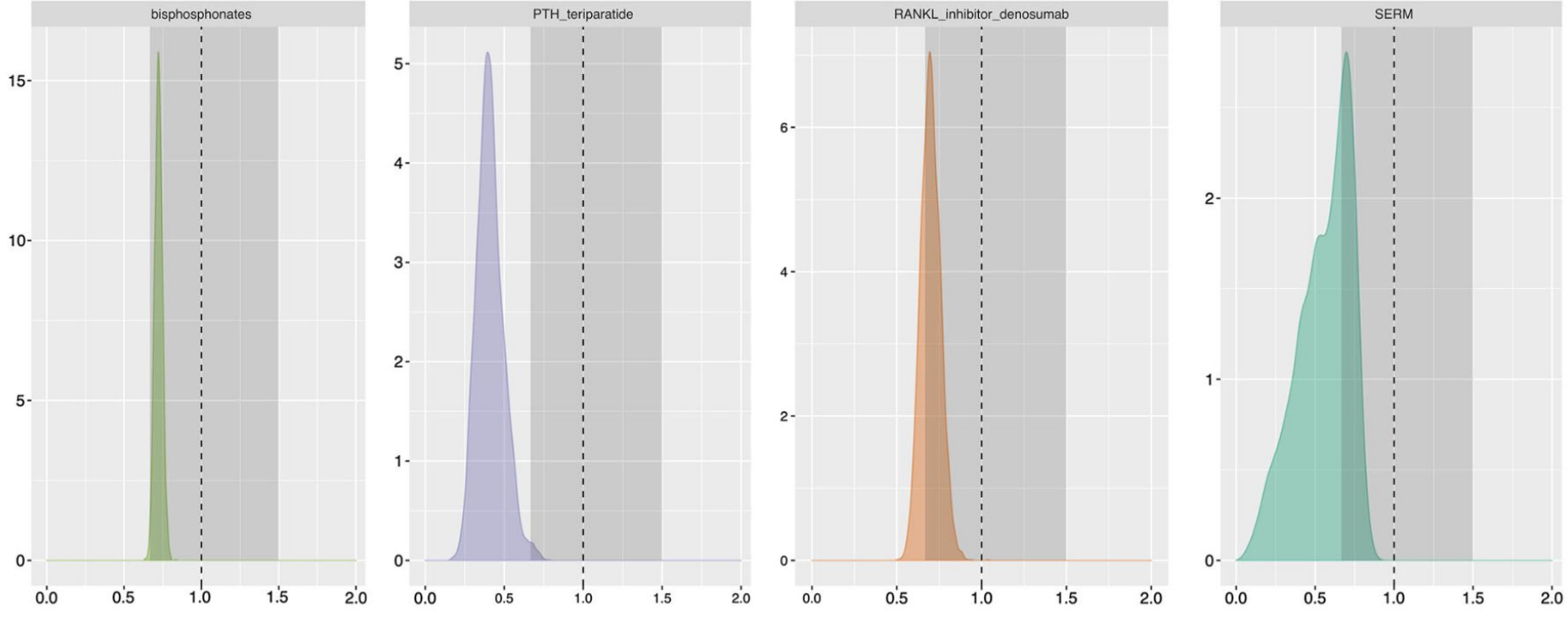
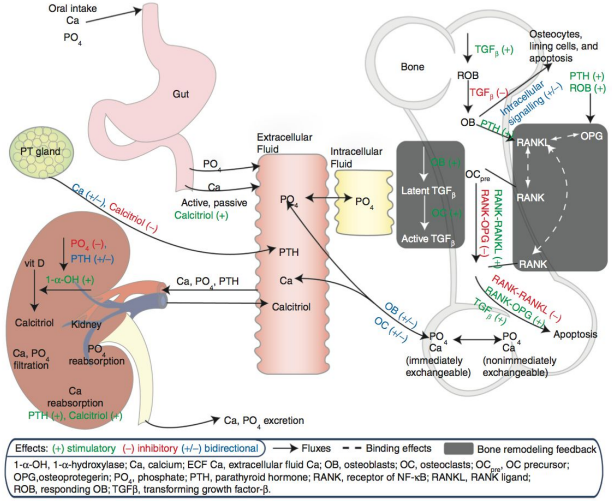


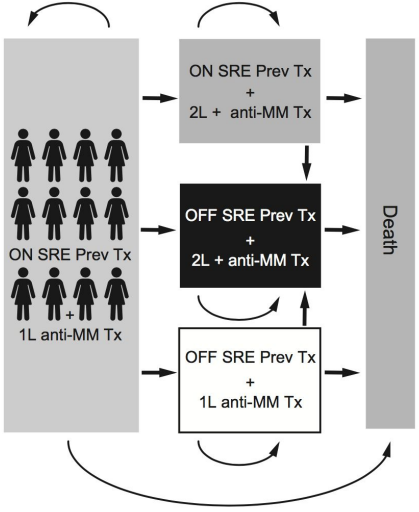
Fig. 3 Hazard ratios for each treatment relative to placebo calculated and density plots for this calculation over the posterior distribution of parameter estimates are represented, for the model with both drug–BMD interaction and additional drug effect

RJ Eudy-Byrne, W Gillespie, MM Riggs, MR Gastonguay. A model of fracture risk used to examine the link between bone mineral density and the impact of different therapeutic mechanisms on fracture outcomes in patients with osteoporosis J Pharmacokinet Pharmacodyn (2017) 44:599–609

Linking MSSP/Fracture Model & Pharmacoeconomics

Quantitative Systems Pharmacology Modeling





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Early Development ICER ($/QALY) Predictions

- New drug, target
- New dose, regimen
- Combination therapies

PMX and PE Model for Hypothetical COPD Drug

Model-Based Meta Analysis

VALUE IN HEALTH 19 (2016) 1026–1032

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Translating Pharmacometrics to a Pharmacoeconomic Model of COPD

Julia F. Slejko, PhD[1,], Richard J. Willke, PhD[2], Jakob Ribbing, PhD[3], Peter Milligan, PhD[4]*

"A hypothetical anti-inflammatory drug that increased FEV1 by 50 ml decreased exacerbations by 26%. Given a simplified estimation of costs and quality-adjusted life-years (QALYs) associated with COPD, a drug with a 50-ml increase priced at €35/mo had an incremental cost effectiveness ratio ranging from €13,000/QALY to approximately €207,000/QALY across patient severity subgroups."

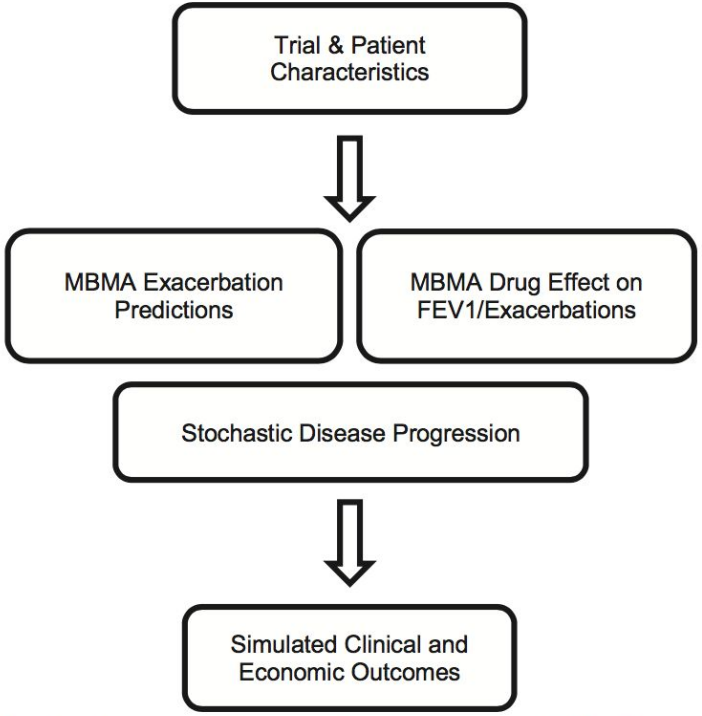


Fig. 1 – Conceptual framework to incorporate MBMA into pharmacoeconomic model. FEV_1, forced expiratory volume in 1 second; MBMA, model-based meta-analysis.

Linking Methods to Extend Inferences

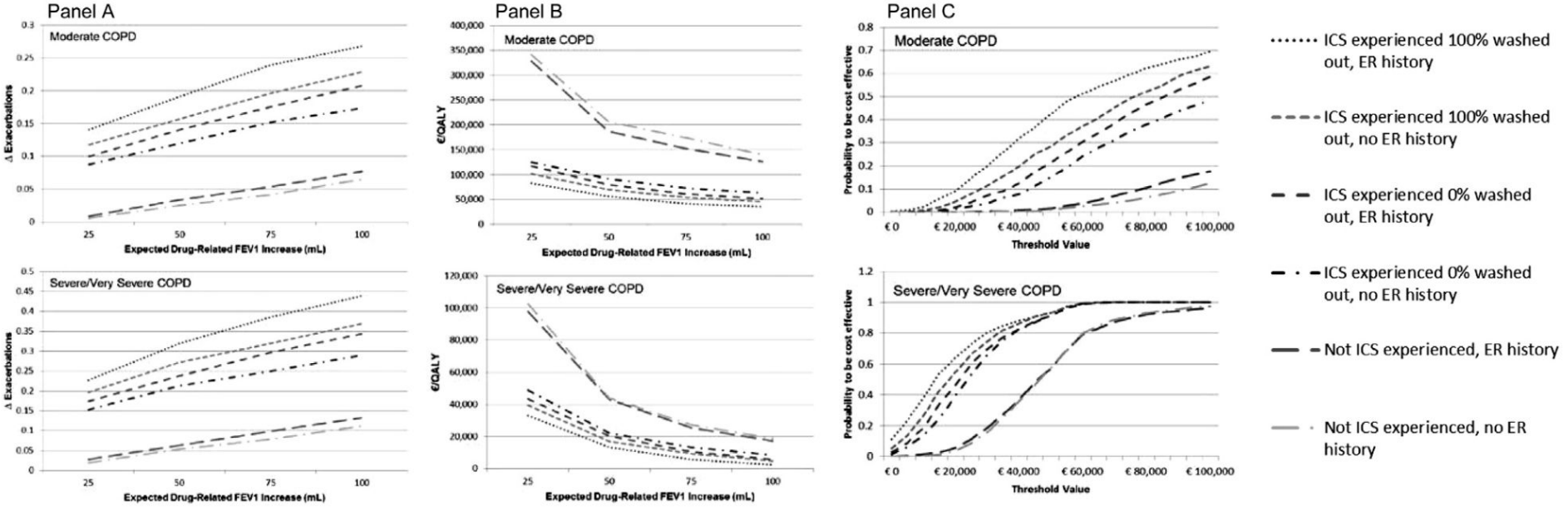


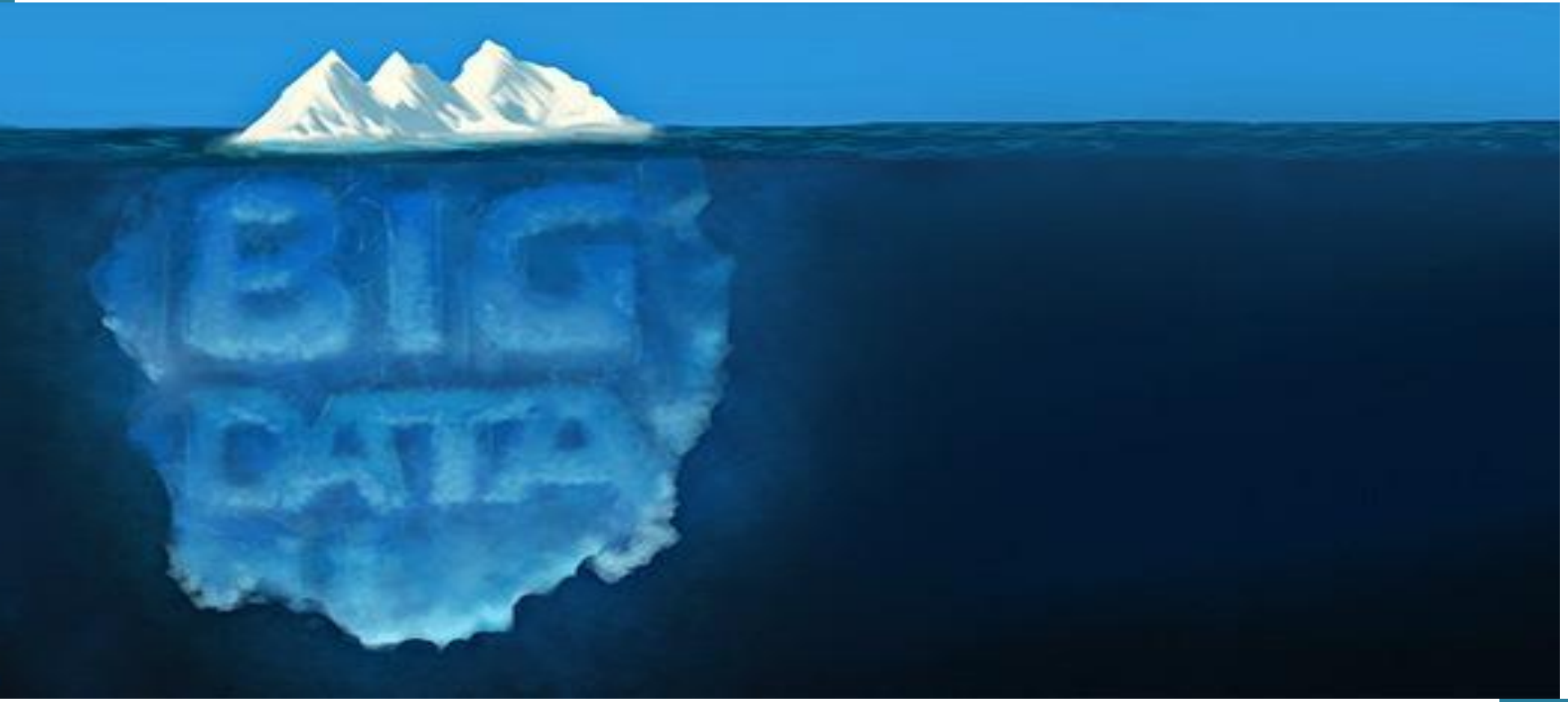
Fig. 3 – (A) Changes in mean exacerbations per treated subject vs. placebo, by scenario subgroup and expected drug effect. (B) ICERs by scenario subgroup and expected drug effect. (C) Acceptability curves by scenario subgroup. COPD, chronic obstructive pulmonary disease; ER, exacerbation rate; FEV_1, forced expiratory volume in 1 second; ICER, incremental cost-effectiveness ratio; ICS, inhaled corticosteroid; QALY, quality-adjusted life-year.

Discussion Points

- The prior examples demonstrate the potential synergy between commonly applied drug development modeling and simulation methods (model based meta-analysis, individual PK-PD, QSP) and economic/outcomes assessments.

- What are other opportunities to inform decision making at the intersection of quantitative disciplines?

Do We Really Know What Lies Beneath the Surface?



http://timoelliott.com/blog/2013/06/the-ethics-of-big-data-vendors-should-take-a-stand.html

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http://timoelliott.com/blog/2013/06/the-ethics-of-big-data-vendors-should-take-a-stand.html

Big Data: Correlation vs. Causation

Scientists are trained to recognize that correlation is not causation. Petabytes allow us to say: ‘Correlation is enough’.

Chris Anderson, 2008

In hiring decisions, what if algorithm predicts that males will be better employees?

“Models that ignore causation can add to historical problems instead of addressing them.”

R. Schutt & C. O’Neil.
Doing Data Science. 2013.

http://www.nytimes.com/2015/06/26/upshot/can-an-algorithm-hire-better-than-a-human.html

BIG DATA is not equal to ALL DATA

- > 20 million posts between Oct. 27 and Nov. 1, 2012
- Study combined hurricane Sandy-related Twitter and Foursquare data

Conclusions:

- Grocery shopping peaked the night before the storm
- Nightlife picked up the day after the hurricane

Most tweets about Sandy came from Manhattan, very few messages originated from Jersey shore.

http://photos.nj.com/star-ledger/2012/11/hurricane_sandy_before_and_aft_7.html The Hidden Biases in Big Data. Kate Crawford. Harvard Business Review https://hbr.org/2013/04/the-hidden-biases-in-big-data/

More Thoughts on Big Data

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **81** 804–806 804

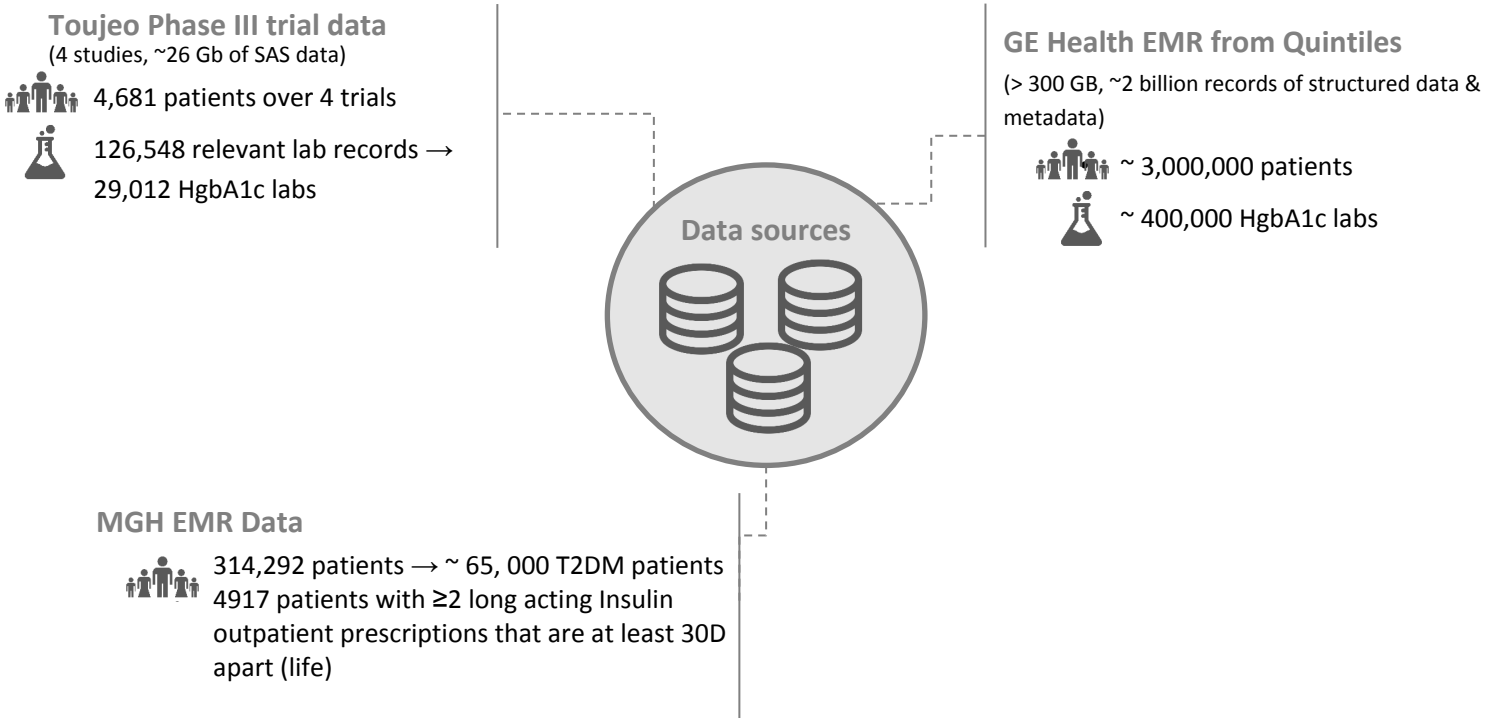
EDITORIAL

Big Data: Challenges and opportunities for clinical pharmacology

Received 29 January 2016; **accepted** 29 January 2016

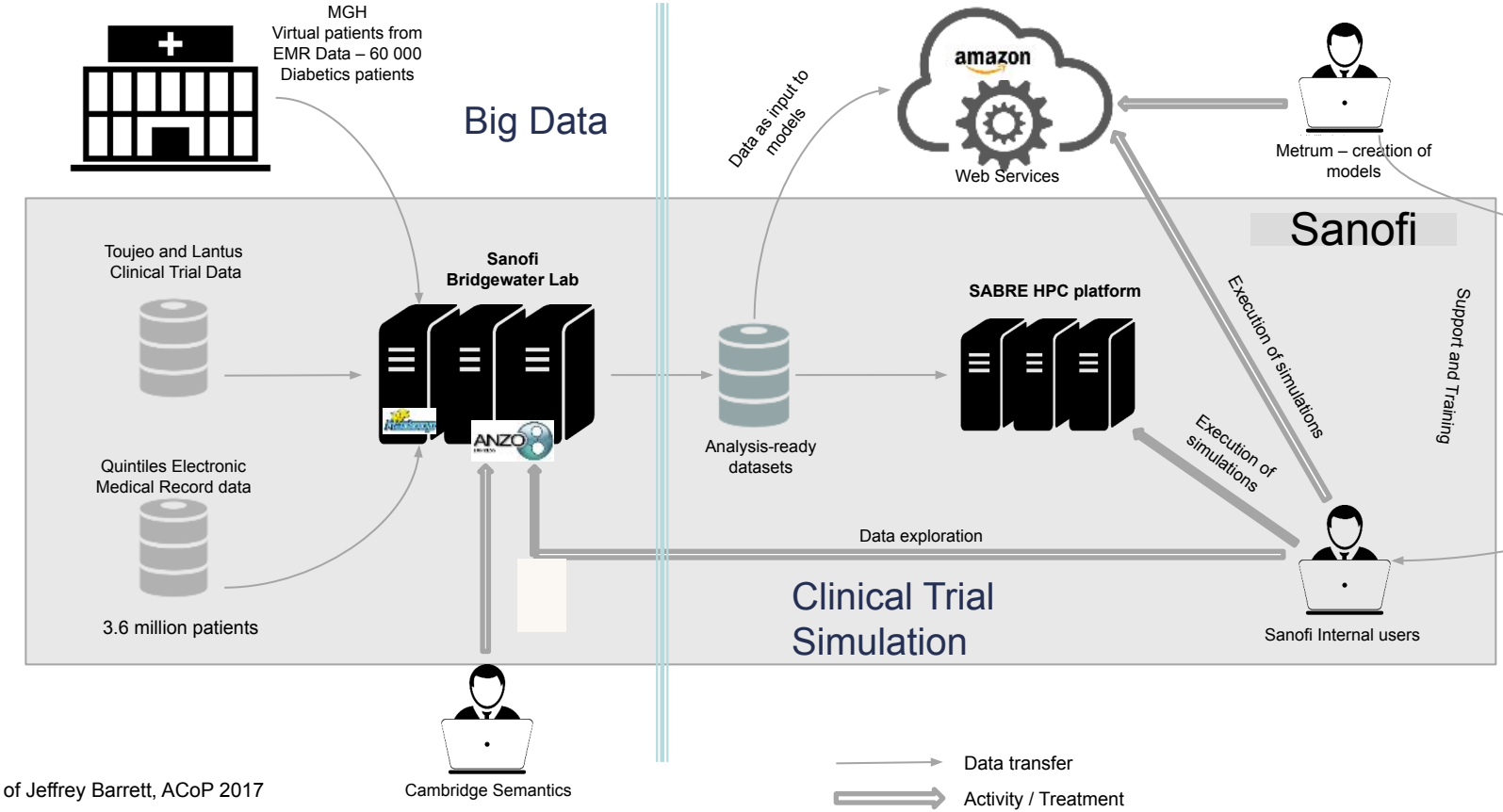
David Flockhart[1], Robert R. Bies[2], Marc R. Gastonguay[3] and Sorell L. Schwartz[4]

Toujeo Real World Evidence Trial Simulation: Data Sources

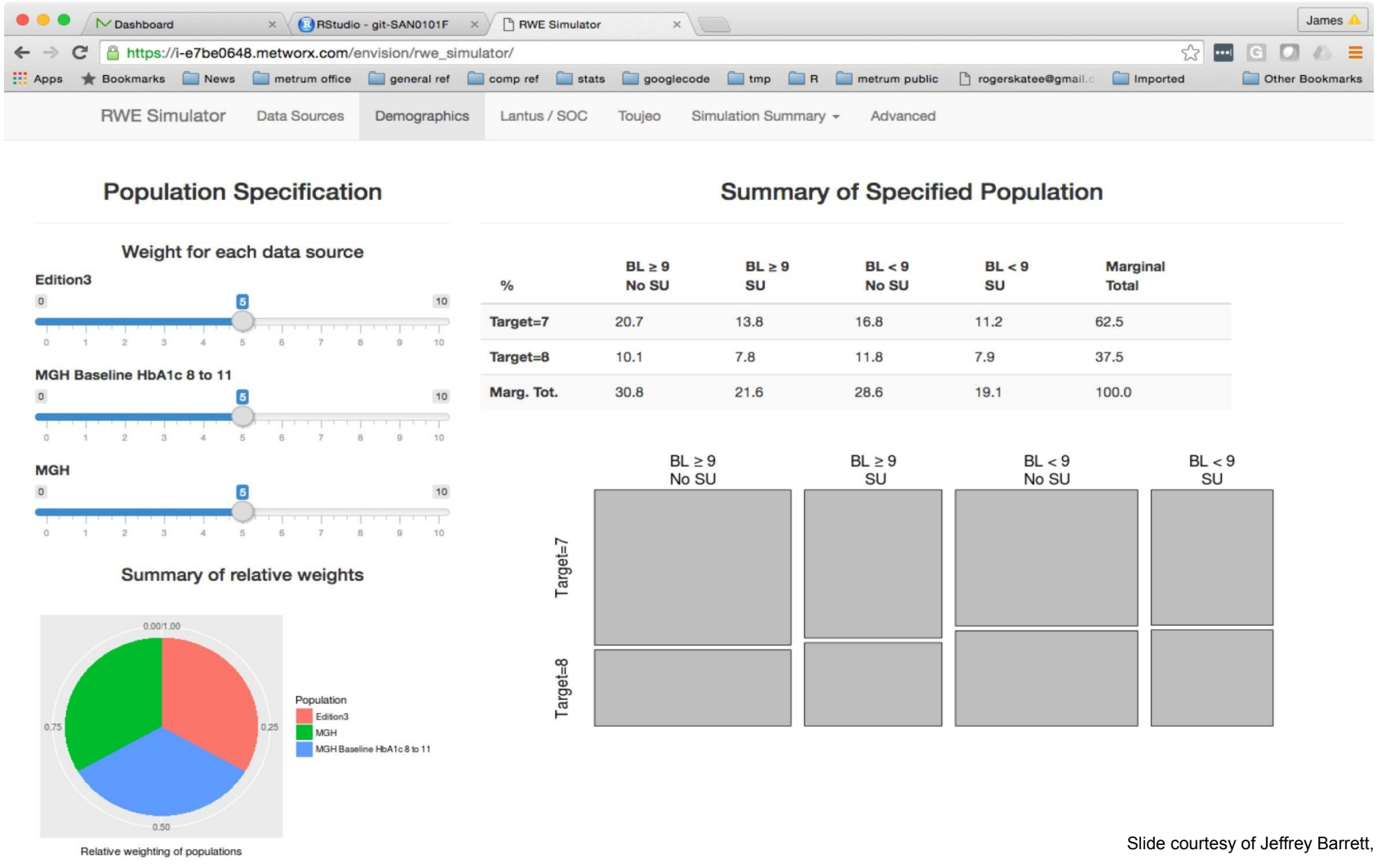


Slide courtesy of Jeffrey Barrett, ACoP 2017

The Big Picture = Systems and Data



Slide courtesy of Jeffrey Barrett, ACoP 2017



Slide courtesy of Jeffrey Barrett, ACoP 2017

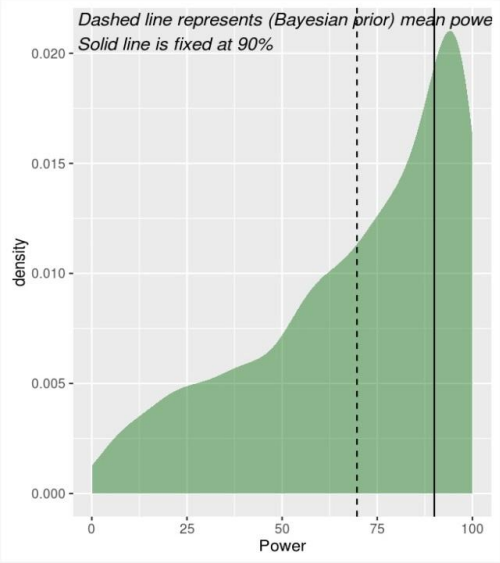
Dashboard | RStudio - git-SAN0101F | RWE Simulator | James

https://i-e7be0648.metworx.com/envision/rwe_simulator/

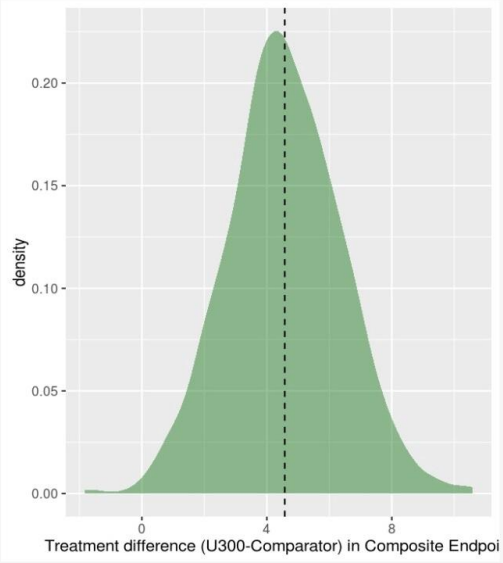
Apps | Bookmarks | News | metrum office | general ref | comp ref | stats | googlecode | tmp | R | metrum public | rogerskatee@gmail.c | Other Bookmarks

RWE Simulator | Data Sources | Demographics | Lantus / SOC | Toujeo | Simulation Summary | Advanced

Probability of Success



Difference in Composite Event Rates



Current Scenario Statistics

	Estimate (%)
Toujeo Composite Endpoint Rate	38.96
Lantus / SOC Composite Endpoint Rate	34.38
Expected Treatment Difference (U300-Comparator)	4.57
Average (Bayesian Predictive) Power	69.70

EDITION 3

Save Scenario

Saved scenarios can be reviewed by toggling to "Multi-scenario Summary" on the Navigation Bar

Slide courtesy of Jeffrey Barrett, ACoP 2017

Dashboard | RStudio - git-SAN0101F | RWE Simulator | James

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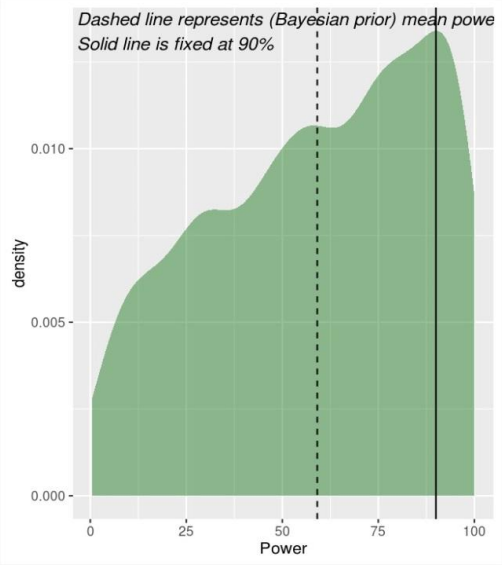
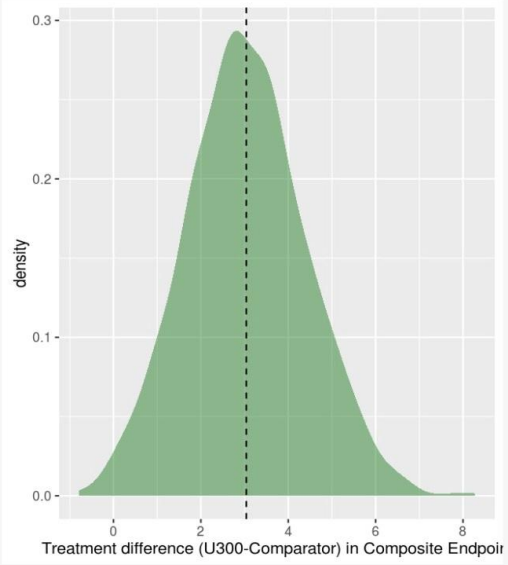
Probability of Success



Difference in Composite Event Rates



Current Scenario Statistics

	Estimate (%)
Toujeo Composite Endpoint Rate	18.68
Lantus / SOC Composite Endpoint Rate	15.64
Expected Treatment Difference (U300-Comparator)	3.04
Average (Bayesian Predictive) Power	59.10

MGH 8-11 with E3 Effect

Save Scenario

Saved scenarios can be reviewed by toggling to "Multi-scenario Summary" on the Navigation Bar

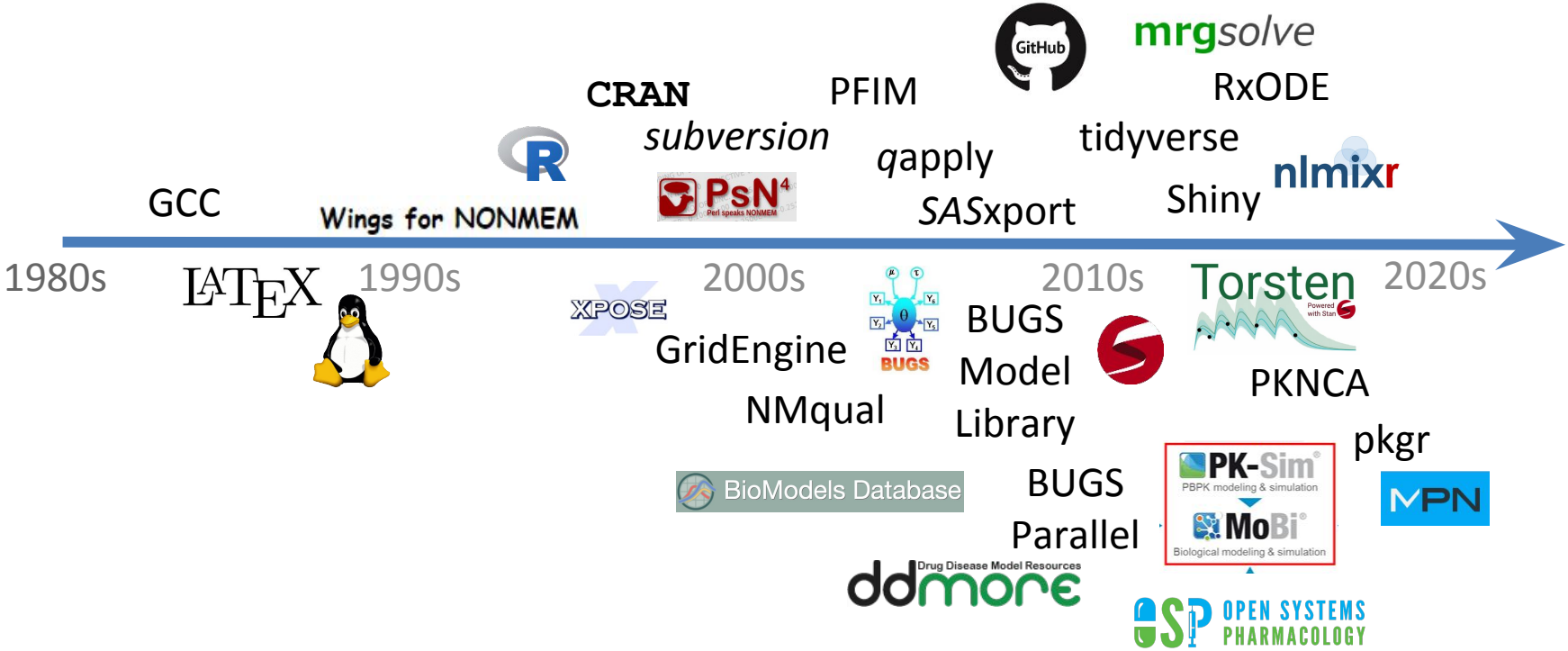
Slide courtesy of Jeffrey Barrett, ACoP 2017

Discussion Point

- How is big (unstructured) data used to inform decisions in your domain?

- What are opportunities to apply those learnings to other drug development and market access decisions?

Open Science in Pharmacometrics



Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

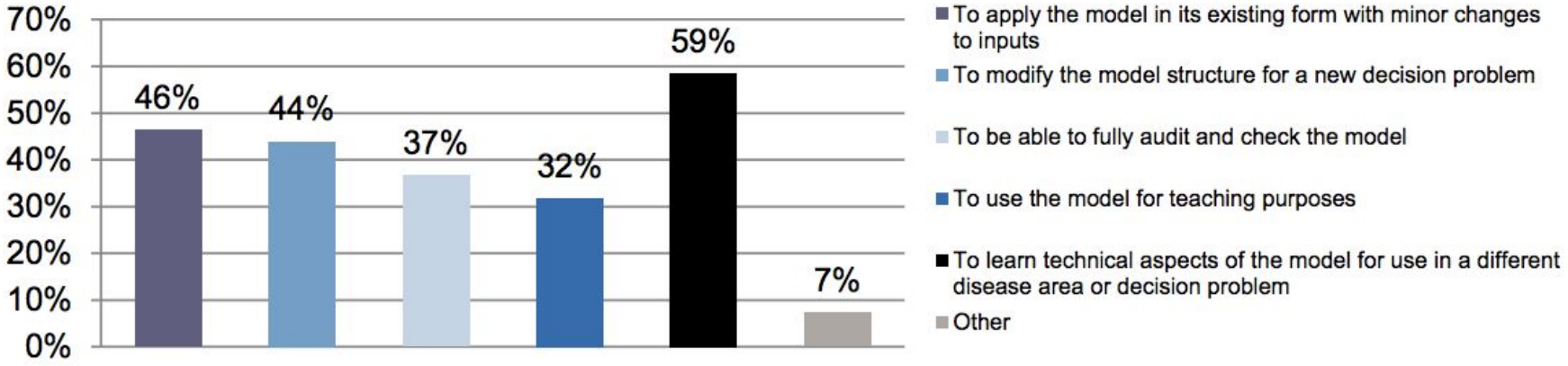
Open Source Models in HEOR

PharmacoEconomics (2017) 35:125–128
DOI 10.1007/s40273-016-0479-8

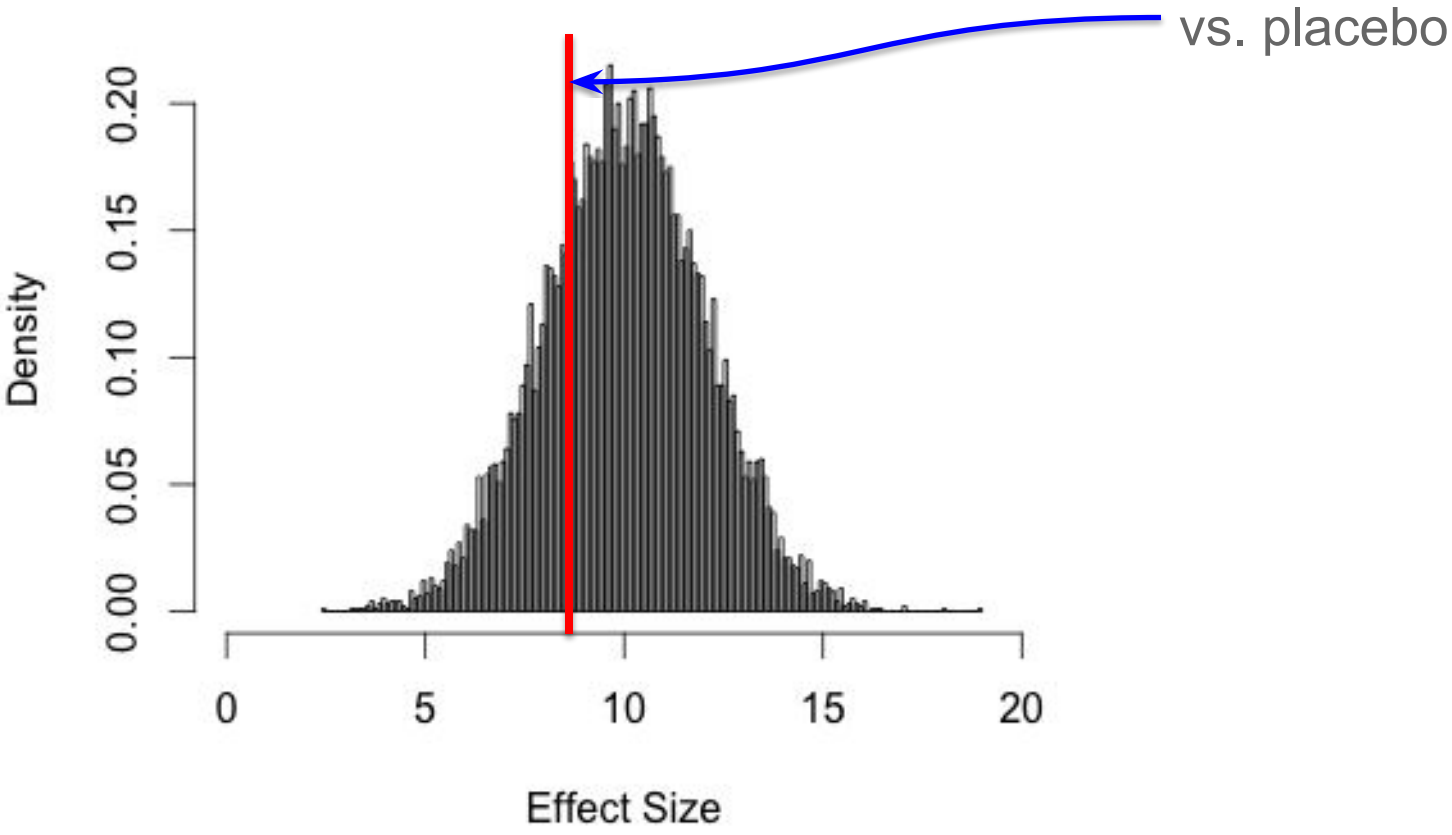
RESEARCH LETTER

Benefits, Challenges and Potential Strategies of Open Source Health Economic Models

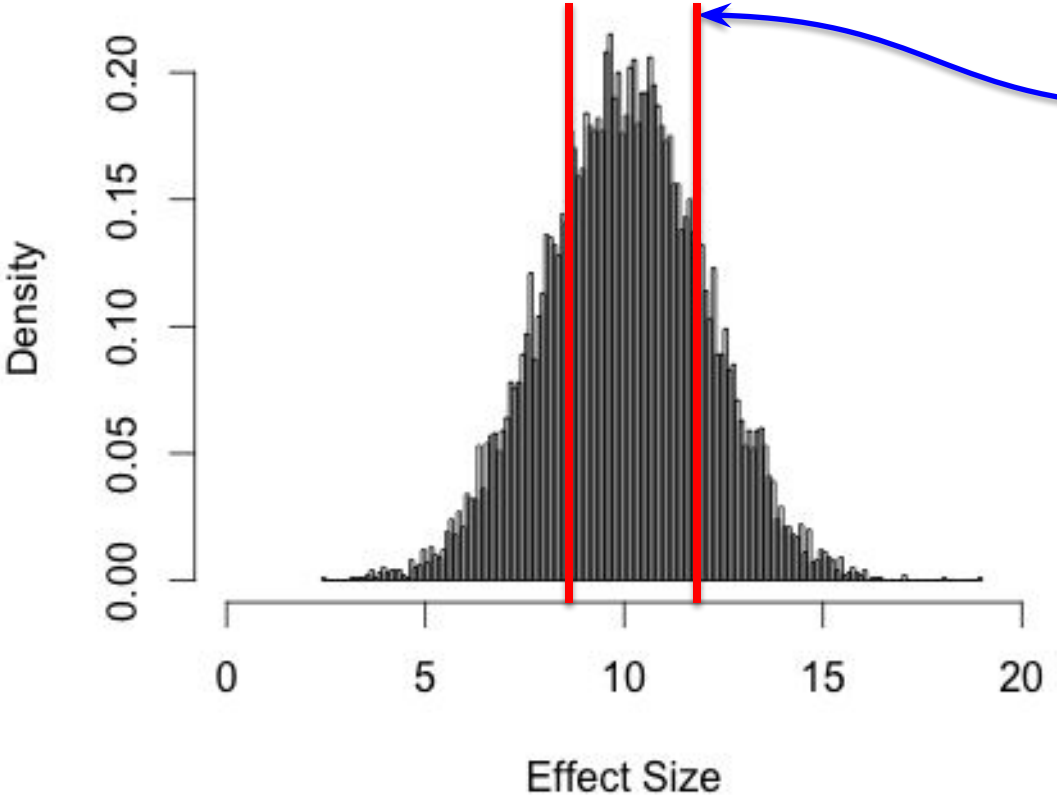
William C. N. Dunlop[1] · Nicola Mason[2] · James Kenworthy[1] · Ron L. Akehurst[2]



Probability of Success: Outdated Thinking

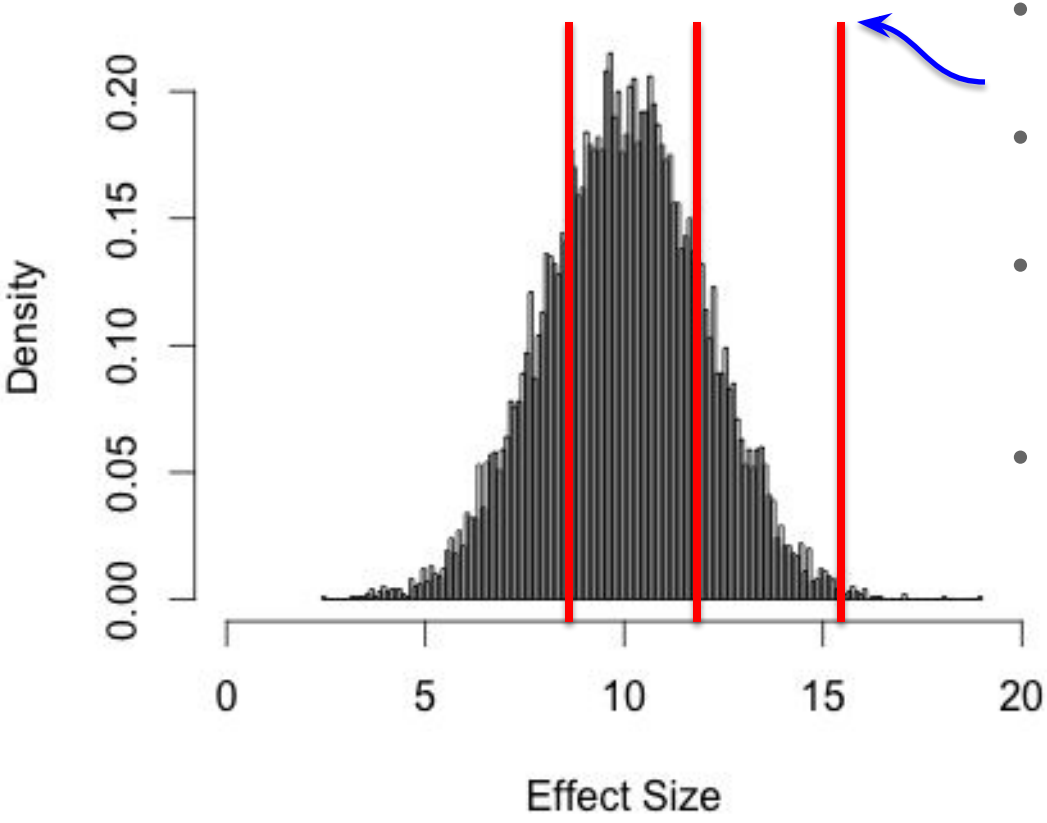


Probability of Success: Evolving Thinking



vs. active control

Probability of Success: New Opportunity



- vs. future competitor
- informed by predicted ICER
- in Real World treatment population
- Continuously updated and re-assessed as development programs and standard of care evolve

Vision for Cross-Discipline Quantitative Platform

Computational & Systems Biology, Pharmacology | Pharmacometrics | Statistics, Data Science | HEOR | Pharmacoepi

Discussion Points

- Are open models used in your work? Why or why not?
- How could a unified data & analytics platform improve collaborations across disciplines?
- What are the challenges related to implementing such a system?

Opportunities for Informed Decision-Making