Real World Evidence in Pharma: Best Practices and Innovations

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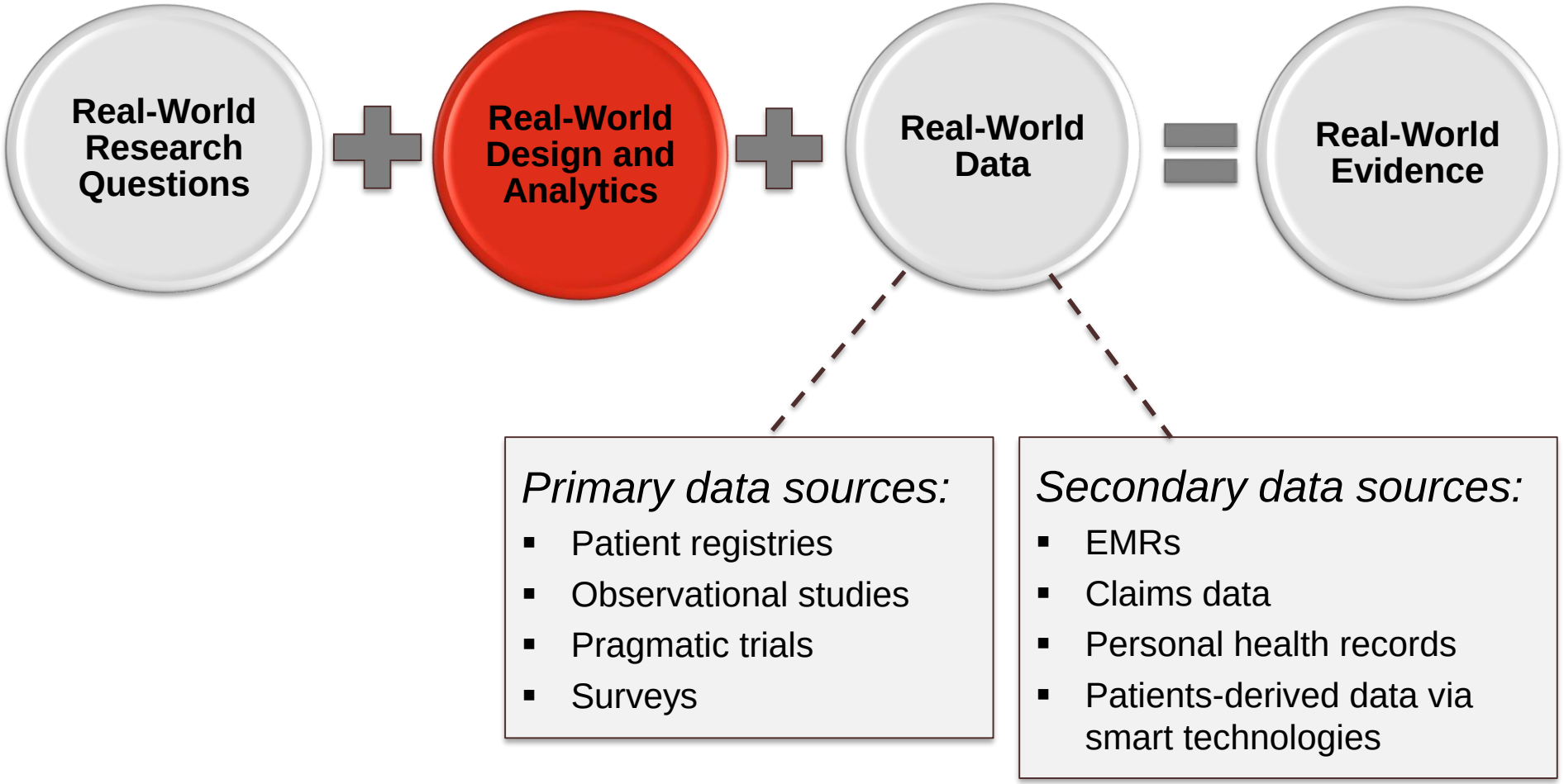
Lilly

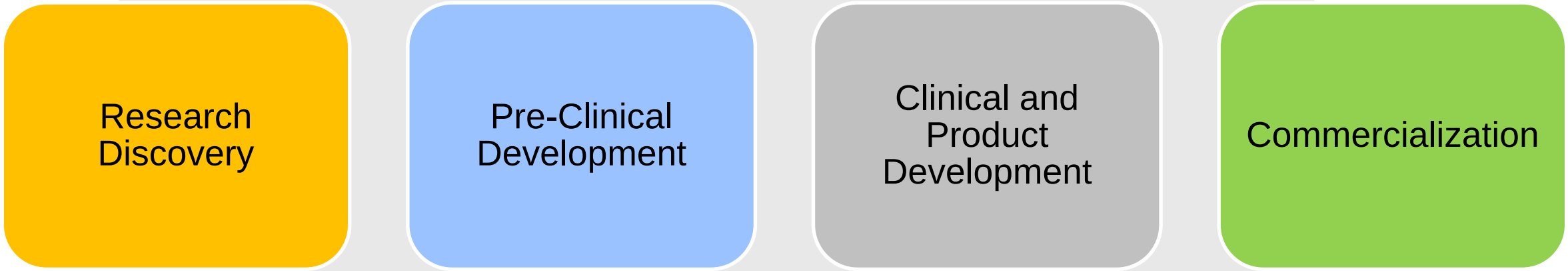
Outline

- RWE across the lifecycle at Pharma
- Focus on Comparative Effectiveness
  - How are we doing?
  - Growing Regulatory Interest
  - Guidance
- Innovation
  - Bias Control
  - Unmeasured Confounding
  - Personalized Medicine

What is Real World Evidence?



RWE Across the Drug Development Process

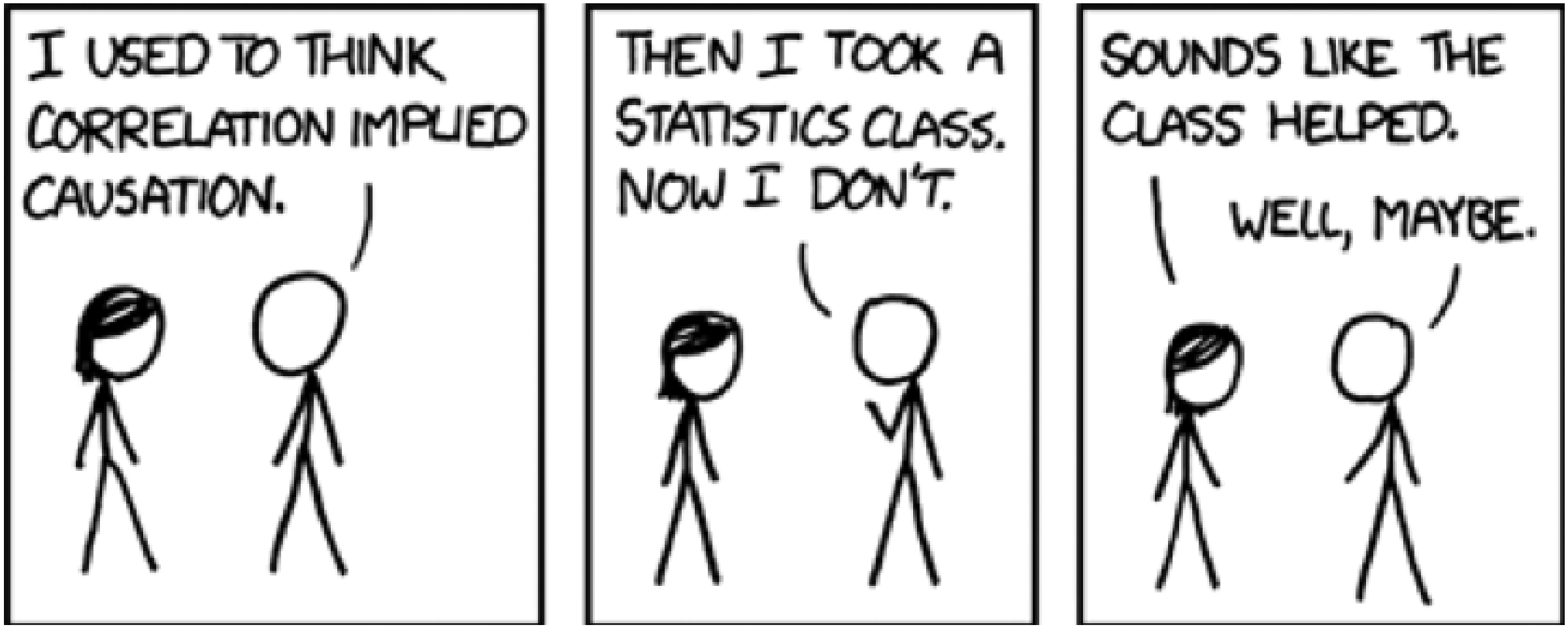


Epidemiologic Studies:
- Natural disease history
- Target population attributes
- Patient-Caregiver outcomes
- Costs
- Treatment Patterns
- Standard of Care

RCT Phase
- Competitor profile (safety, effectiveness, cost, adherence, …)
- PRO development / validation
- RCT Planning & Recruitment

Submission Support
- NMA for HTA Submissions
- Cost Effectiveness Models
- Budget Impact Models
- QOL
- Base Rates – Safety
- Concurrent controls

Launch and Commercialization
- Comparative Effectiveness
- Precision Medicine
- Safety Monitoring
- FDAMA114
- Value & Access Support
  - Value based contracts
  - Usual Care Outcomes: costs, adherence, outcomes, populations
  - Policy



NAS Report (2018): The Irreproducibility Crisis of Modern Science: Causes, Consequences, and the Road to Reform

RWE Guidance Documents: Progress

FDA: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

2004/2007 TREND & STROBE

- Checklists

2009 ISPOR Good Res. Practices

- Design and Reporting (Berger et al); Mitigating Bias (Cox et al); Analytic Methods (Johnson et al)

2010 GRACE

- Dreyer et al (2010); ISPE

2014 PCORI & ISPOR-AMPC-NPC

- Methodology Reports; Flowchart (Berger et al 2014)

2017 Joint ISPOR-ISPE TaskForce

- Berger (2017) & Wang (2017)

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PDUFA VI Commitments

- Enhance use of RWE in regulatory decision making
  - **Conduct a public workshop to gather input into topics related to the use of RWE for regulatory decision-making**
  - **Initiate appropriate activities (e.g. pilot studies or methodology development projects) to address key issues …**
  - **Publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions …**

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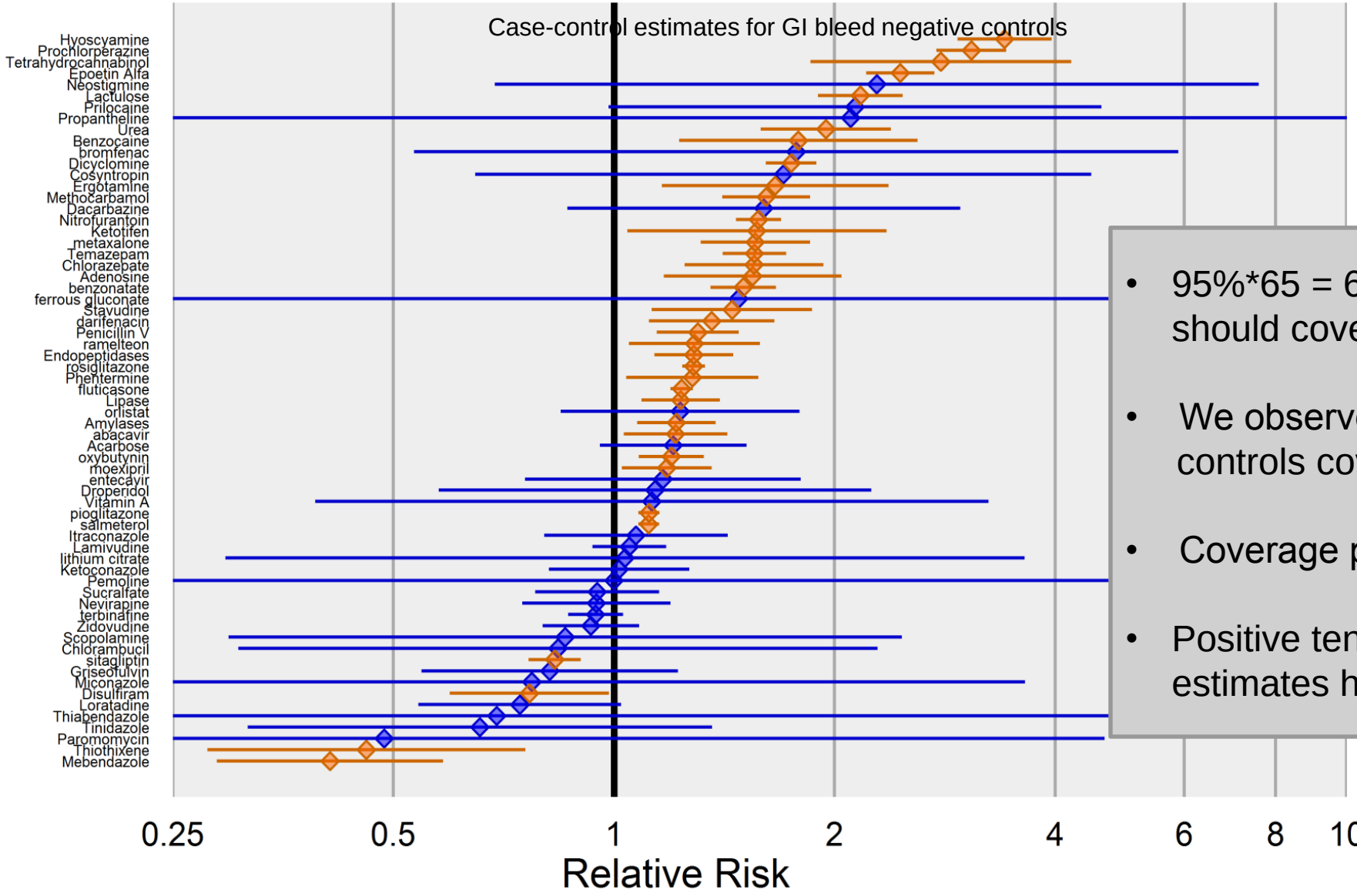
HTA: Innovative Medicines Initiative (GetReal)

How are we Doing (Retrospective RWE)?

OMOP Simulations (Ryan et al 2012)



- 95%*65 = 62 of the CIs should cover RR = 1
- We observed 29 of negative controls covered RR=1
- Coverage probability = **45%**
- Positive tendency: 74% of estimates have RR>1

NEJM 2016: Regulatory Views on RWE for Decision Making

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Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

"Although …… important progress is being made in the methodologic arena, these factors do not yet suffice to fully overcome the fundamental issues of confounding, data quality, and bias, … "

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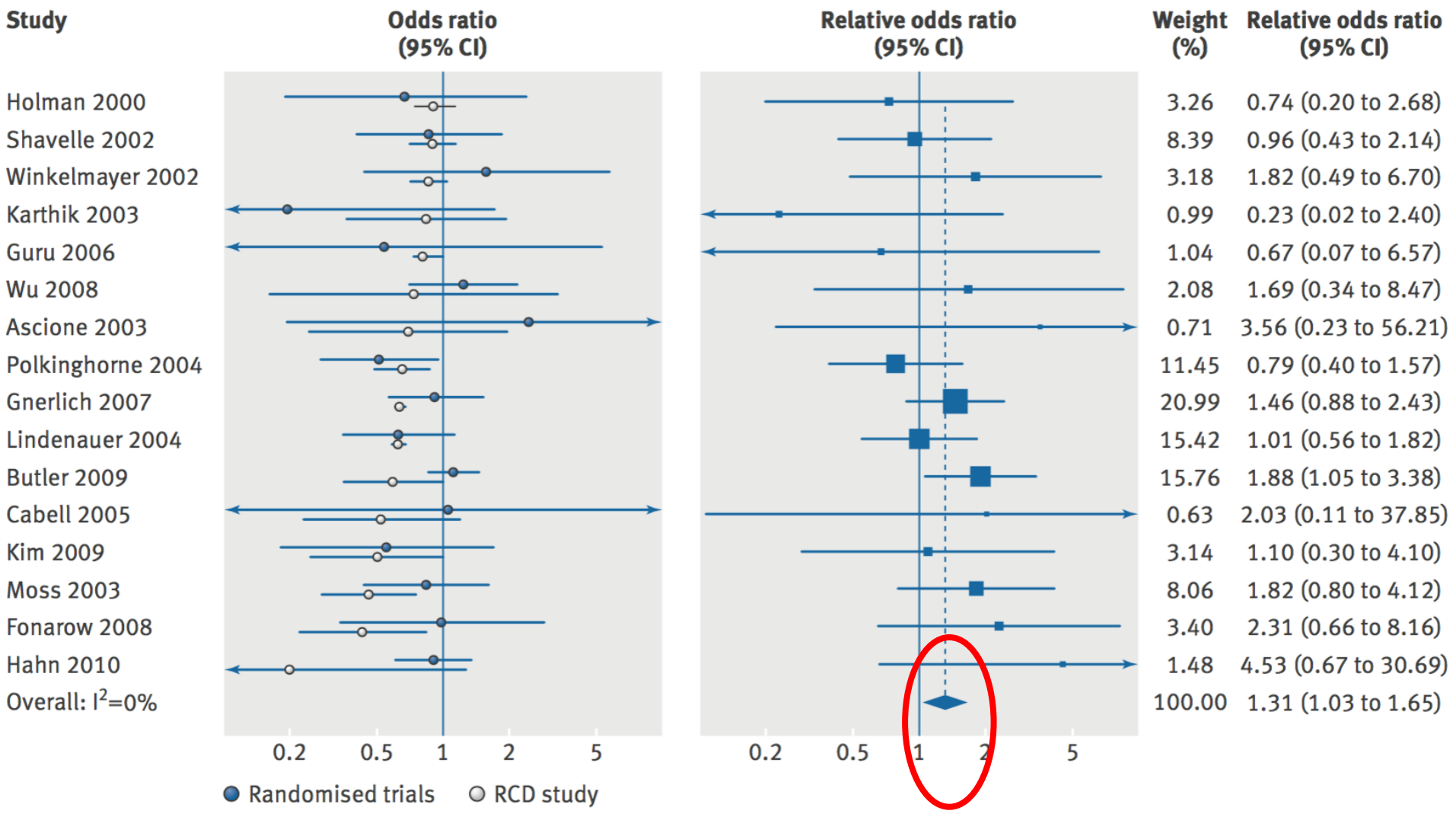
Transforming Evidence Generation to Support Health and Health Care Decisions

Robert M. Califf, M.D., Melissa A. Robb, M.S.(Reg.Sci.), B.S.N., Andrew B. Bindman, M.D., Josephine P. Briggs, M.D., Francis S. Collins, M.D., Ph.D., Patrick H. Conway, M.D., Trinka S. Coster, M.D., Francesca E. Cunningham, Pharm.D., Nancy De Lew, M.A., Karen B. DeSalvo, M.D., M.P.H., Christine Dymek, Ed.D., Victor J. Dzau, M.D., Rachael L. Fleurence, Ph.D., Richard G. Frank, Ph.D., J. Michael Gaziano, M.D., M.P.H., Petra Kaufmann, M.D., Michael Lauer, M.D., Peter W. Marks, M.D., Ph.D., J. Michael McGinnis, M.D., M.P.P., Chesley Richards, M.D., M.P.H., Joe V. Selby, M.D., M.P.H., David J. Shulkin, M.D., Jeffrey Shuren, M.D., J.D., Andrew M. Slavitt, M.B.A., Scott R. Smith, Ph.D., B. Vindell Washington, M.D., M.H.C.M., P. Jon White, M.D., Janet Woodcock, M.D., Jonathan Woodson, M.D., and Rachel E. Sherman, M.D., M.P.H.

"Much of the current excitement about RWE stems from the hope that access to sources of emerging data of adequate quality will, when paired with the development of more robust methods, allow greater use of observational treatment comparisons in drawing causal inferences about the treatment effects of medical products."

RCT vs. RWE (Hemkens et al. BMJ 2016)



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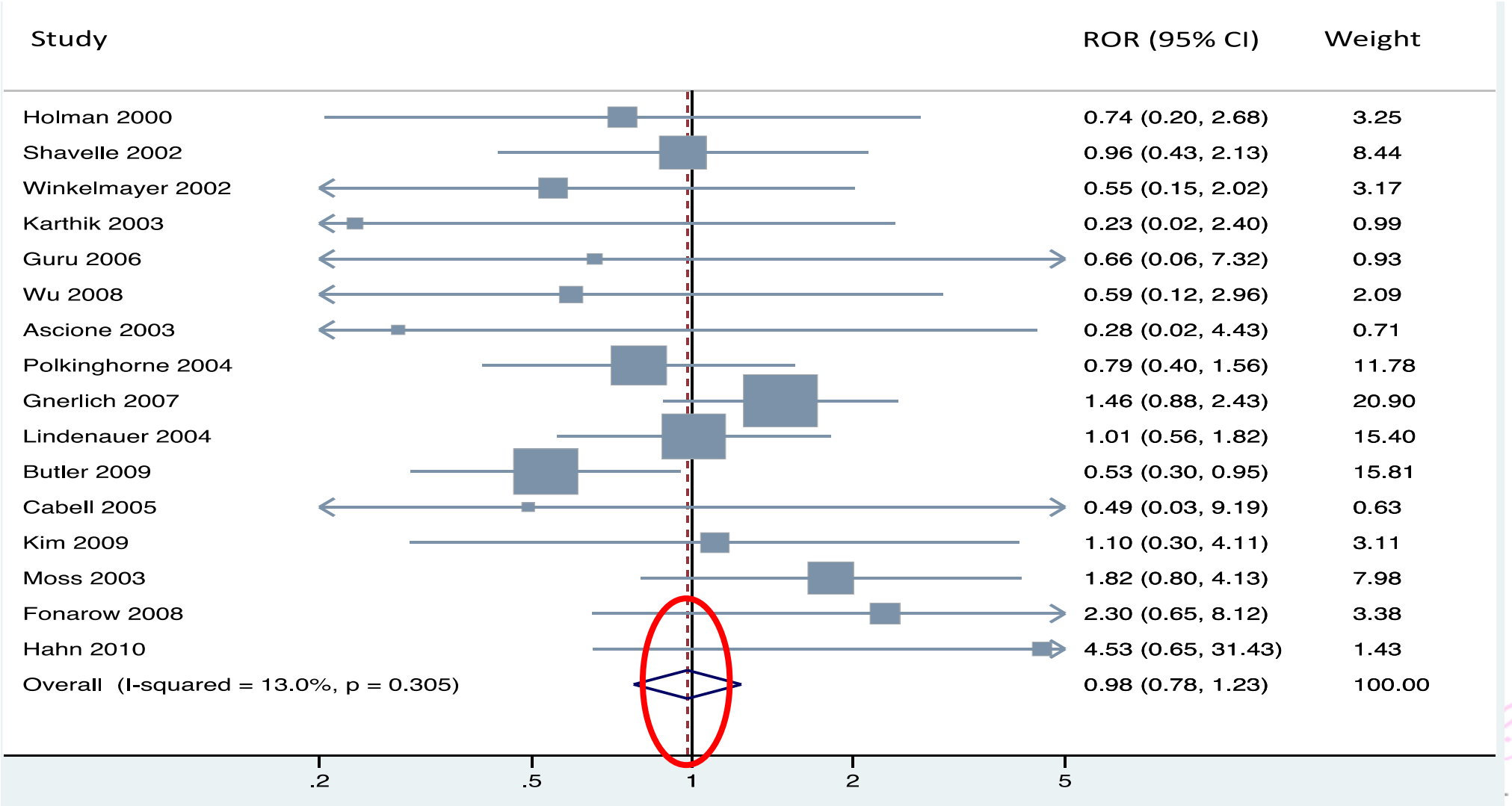
Answers That Matter.

Re-analysis of RCT vs RWE (Franklin et al 2017)

Franklin JM, et al.: A Bias in the Evaluation of Bias Comparing Randomized Trials with Non-experimental Studies. Epidemiology Methods 2017



Interim Summary

We need to improve the foundation – the operating characteristics of RWE – to the point where we can have reliable and valid decision making acceptable to regulatory decision makers

Steps

- Re-Assess where we are at: Operating Characteristics
- Improving our Best Practices
- Growing Opportunities

Real World Data could get a Boost from Trial Replication Project

(Pink Sheet April 30, 2018)

- 'Replicate' 30 RCT (published and ongoing) using Optum, Truven, and Medicare Claims data.

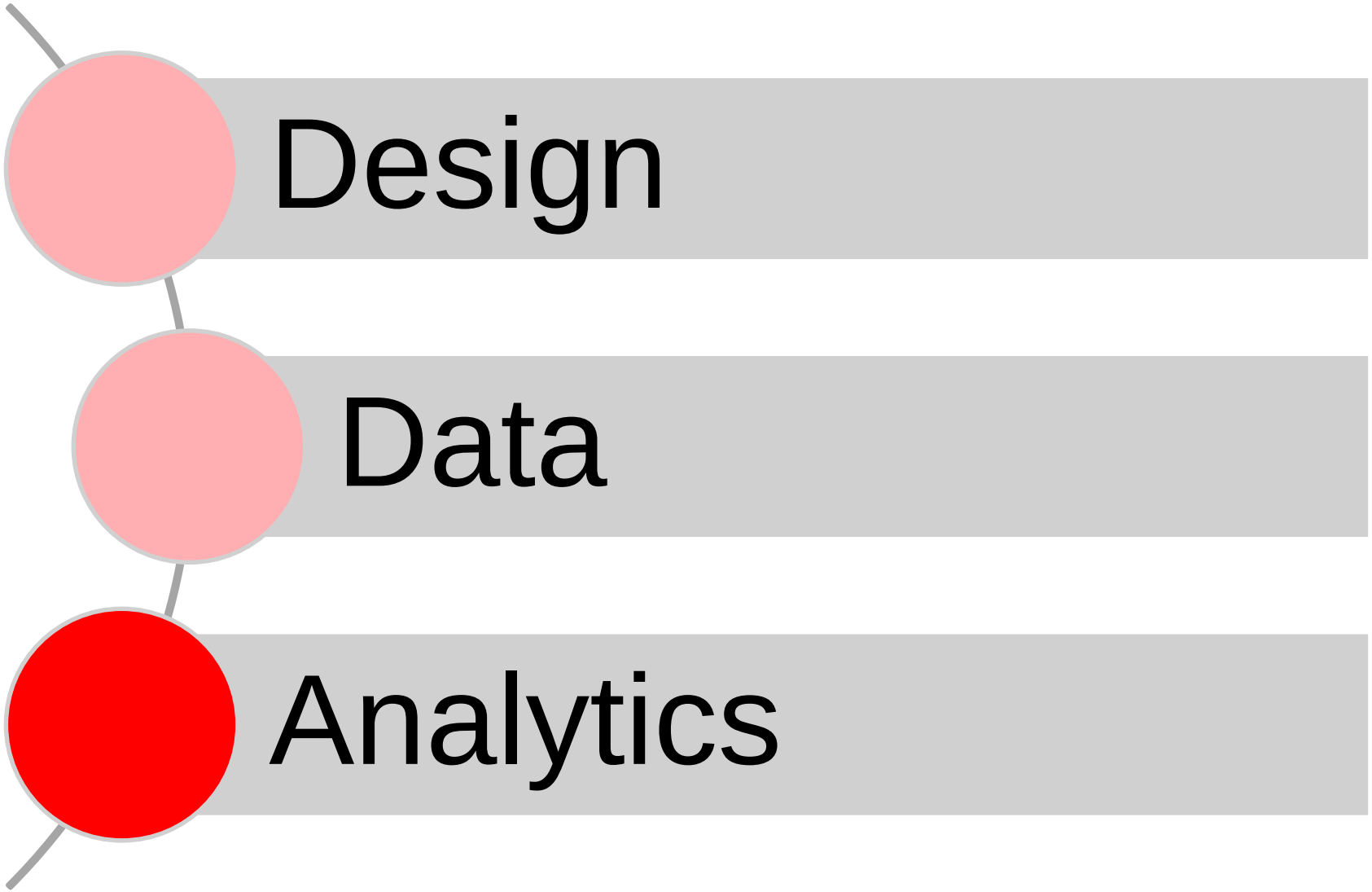
- Funded by FDA; Analyses by Brigham & Women's / Harvard

- Trials in the cardiovascular, endocrinology, musculoskeletal, and pulmonary

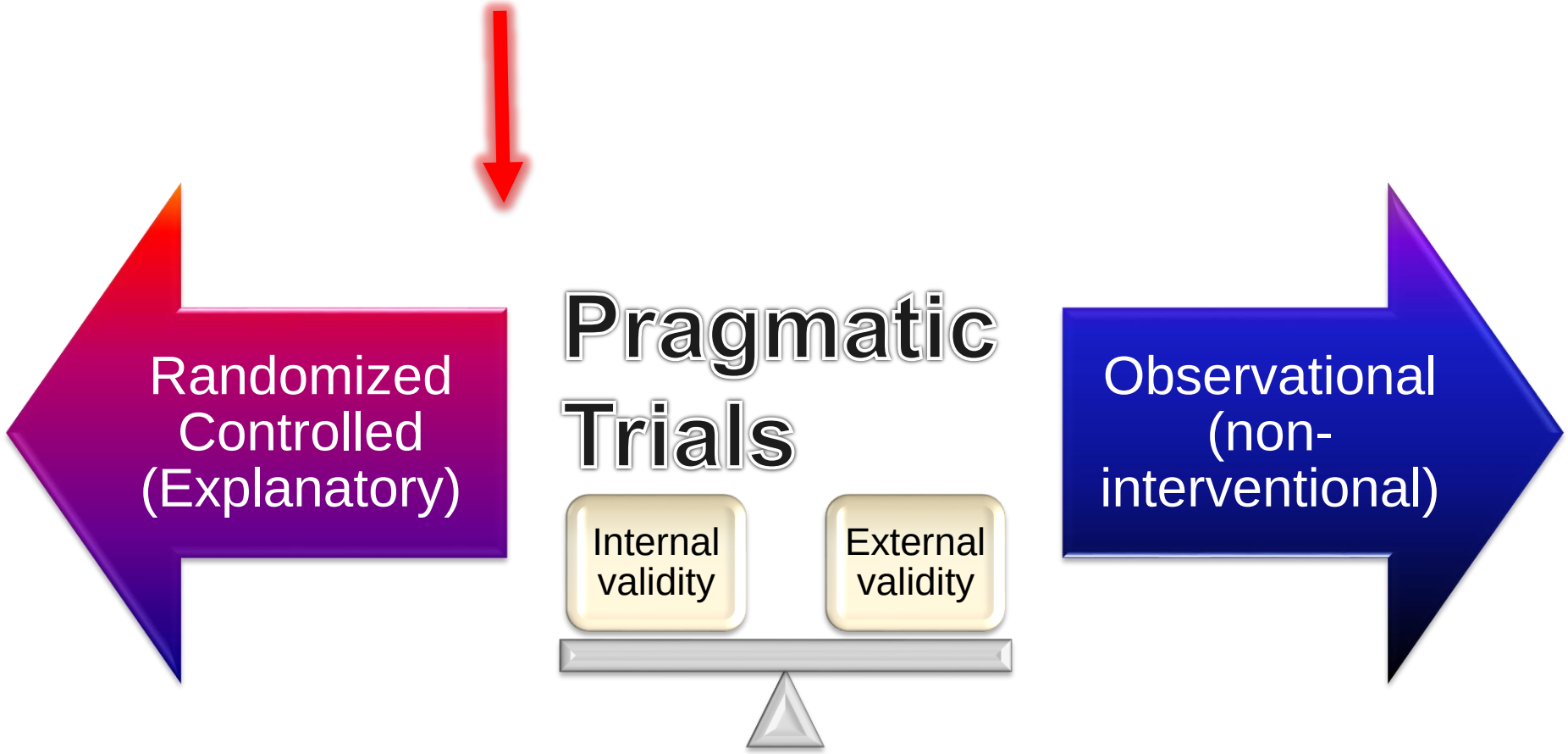
- Not a 'literature survey' …
  Targeted Trial Approach
  Multiple methods

- Questions (Franklin and Schneeweis 2017)
  - When?: When can one study drug effects without randomization?
    (what disease states, data, outcomes, etc)
  - How?: Is some methodology better than others at replicating results?
  - Why?: Why some studies fail to replicate and some do replicate?

How do we get better?



Where does the Evidence Bar Belong??



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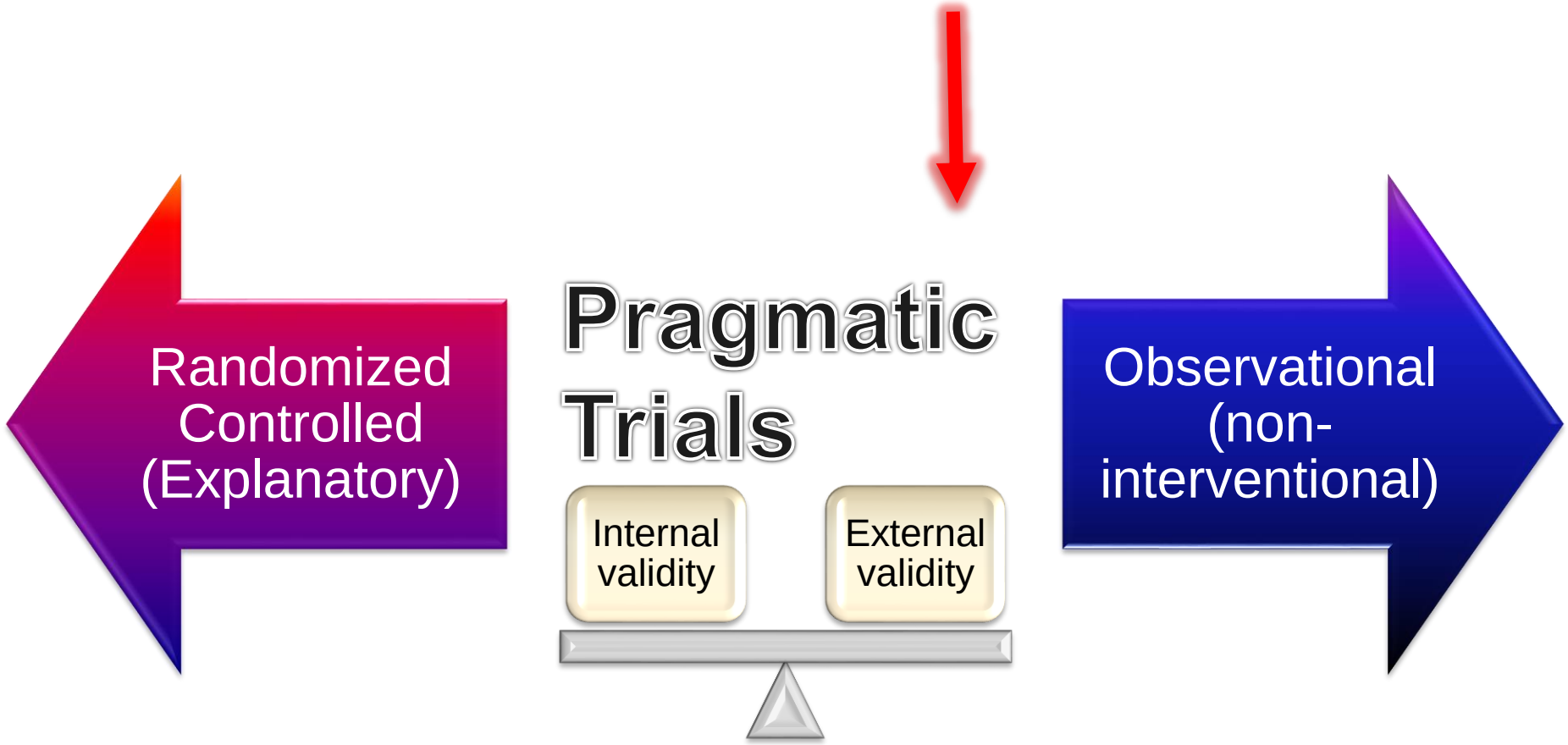
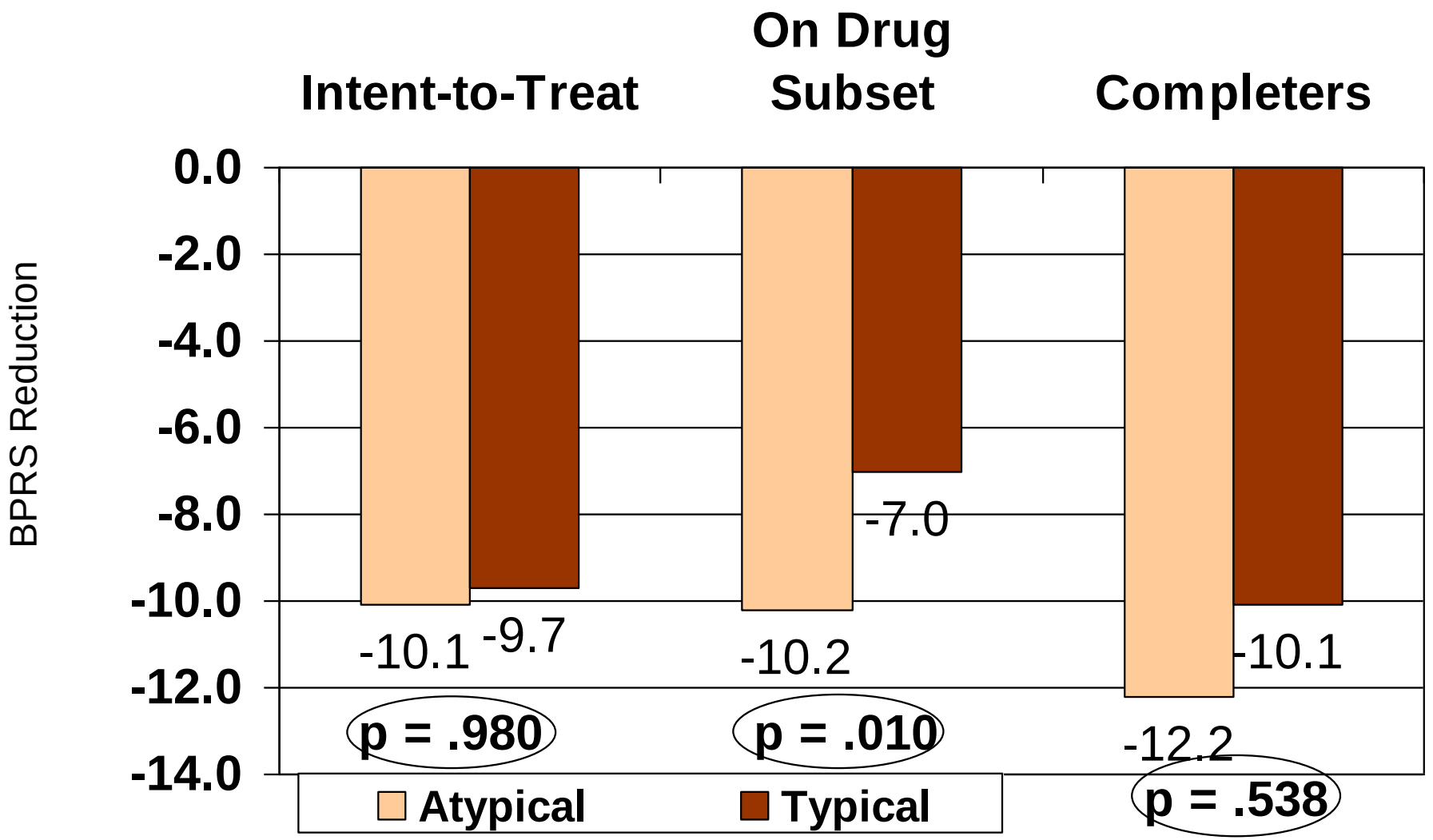


Methods Matter: Pragmatic Example

(Faries et al 2008)

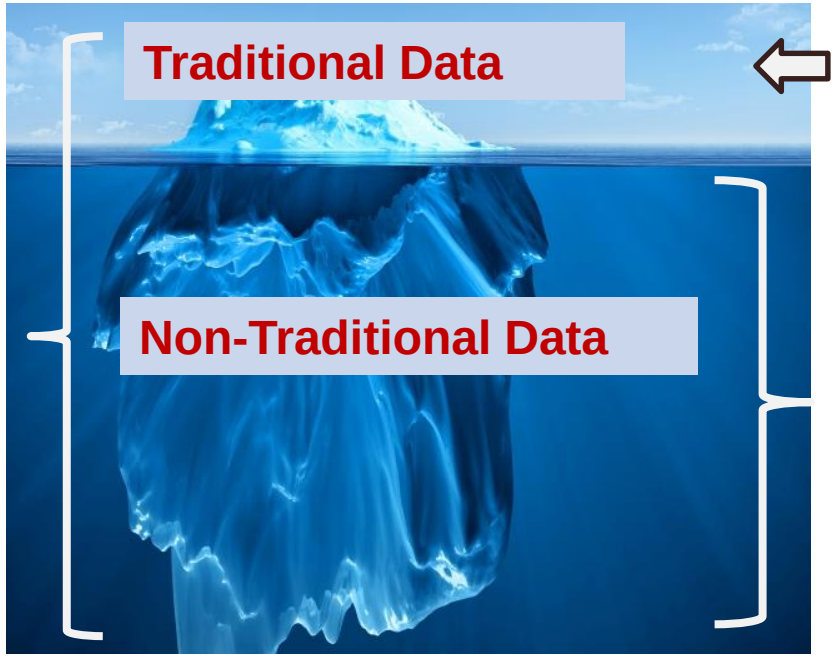


Estimands
- Population
- Intercurrent Events

MSM & G-estimation Methods

Future of BIG DATA in Real World Evidence

Data linked from multiple sources provides a comprehensive view of the patient



EMR , Claims, Registries, Studies and Survey Data

Patient data from mHealth apps, sensors/wearable devices, unstructured medical data, and genomic data

Statistical Challenges in Real World Data Comparative Effectiveness

– With randomization – standard methods produce estimates of causal treatment effects

– Without randomization – standard methods produce only ‘associations’ …. Treatment groups are NOT comparable at baseline thus comparisons are BIASED

#1 Issue: Confounding

Basic Assumptions for Causal Inference

(Rubin's potential outcome framework)

Propensity Score adjustments can provide for estimates of the causal group differences under the following assumptions:

#1 **No Unmeasured Confounders**

All confounders are in the dataset and analysis

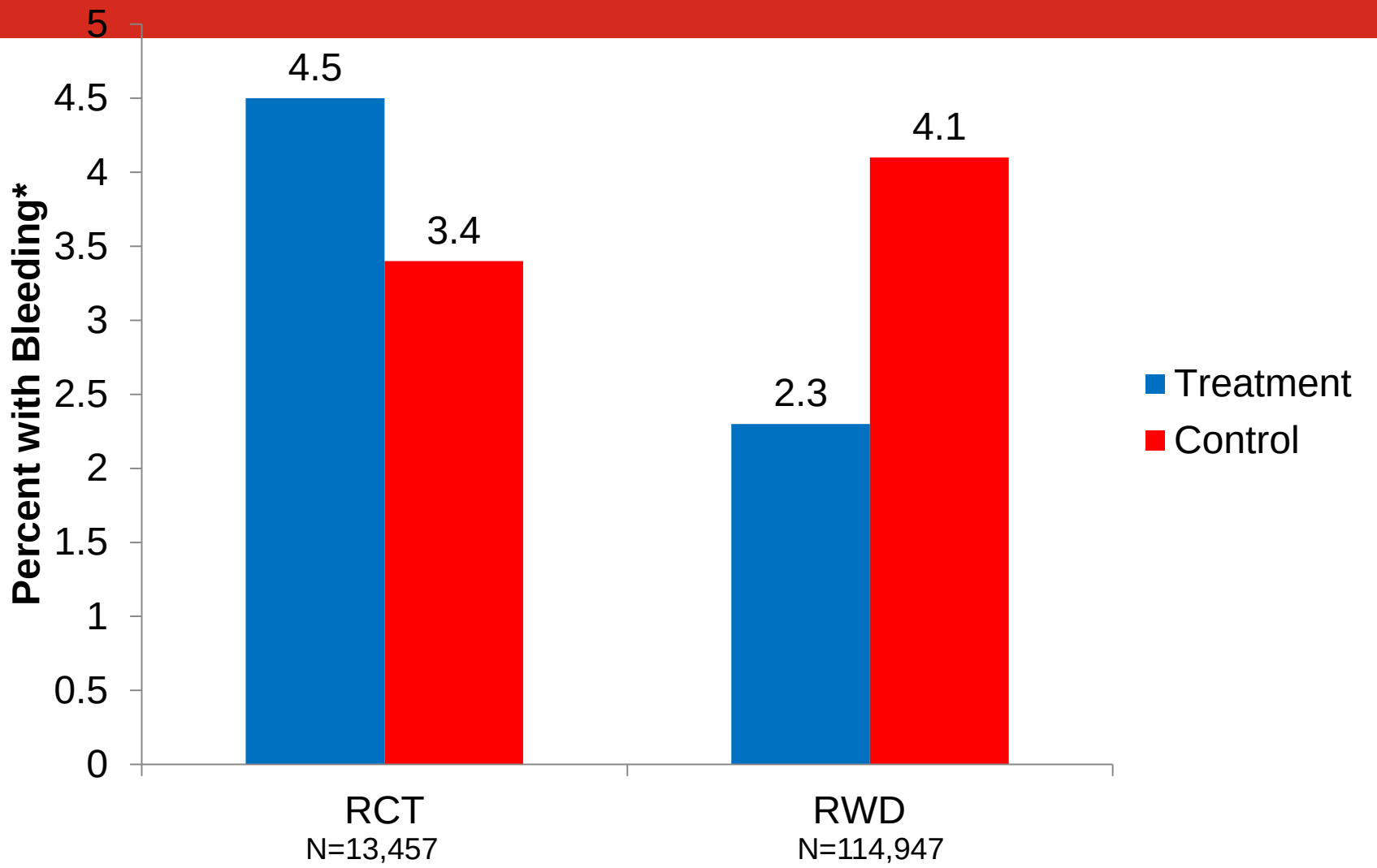
#2 **Sufficient Overlap in Populations**

positivity, no perfect confounding

#3 **Correct Statistical Models**

RCT vs RWD Example

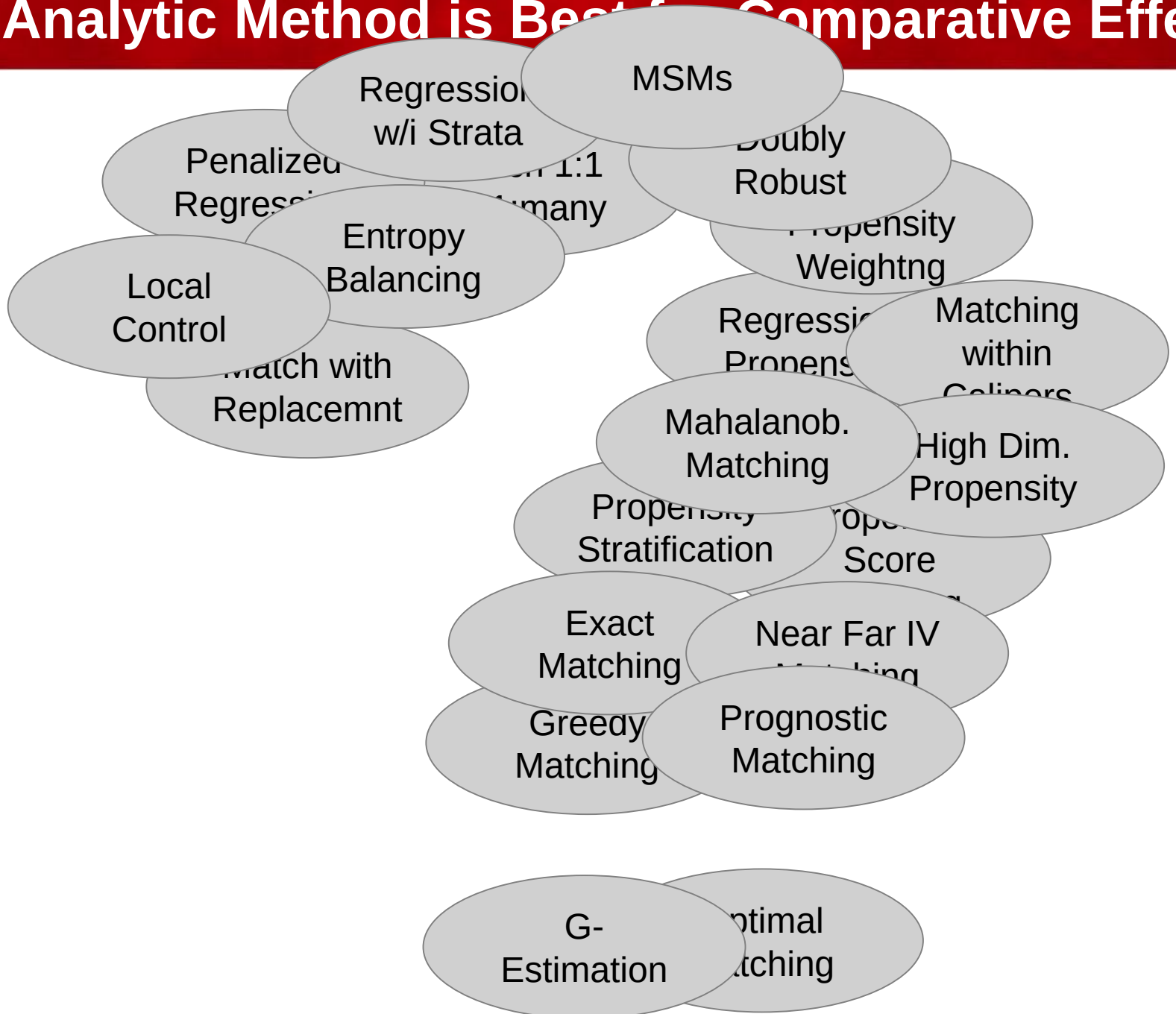
Bleeding Rates ACS-PCI Patients



*RCT: TRITON-TIMI38 [TIMI criteria for major or minor bleeding
*RWD: Premier Database [ICD9 bleeding per Berenson 2010]

- Ernst 2012, QCOR
- Wiviott 2007 NEJM

Which Analytic Method is Best for Comparative Effectiveness?



Bias Control Simulations (Zagar et al. 2017)

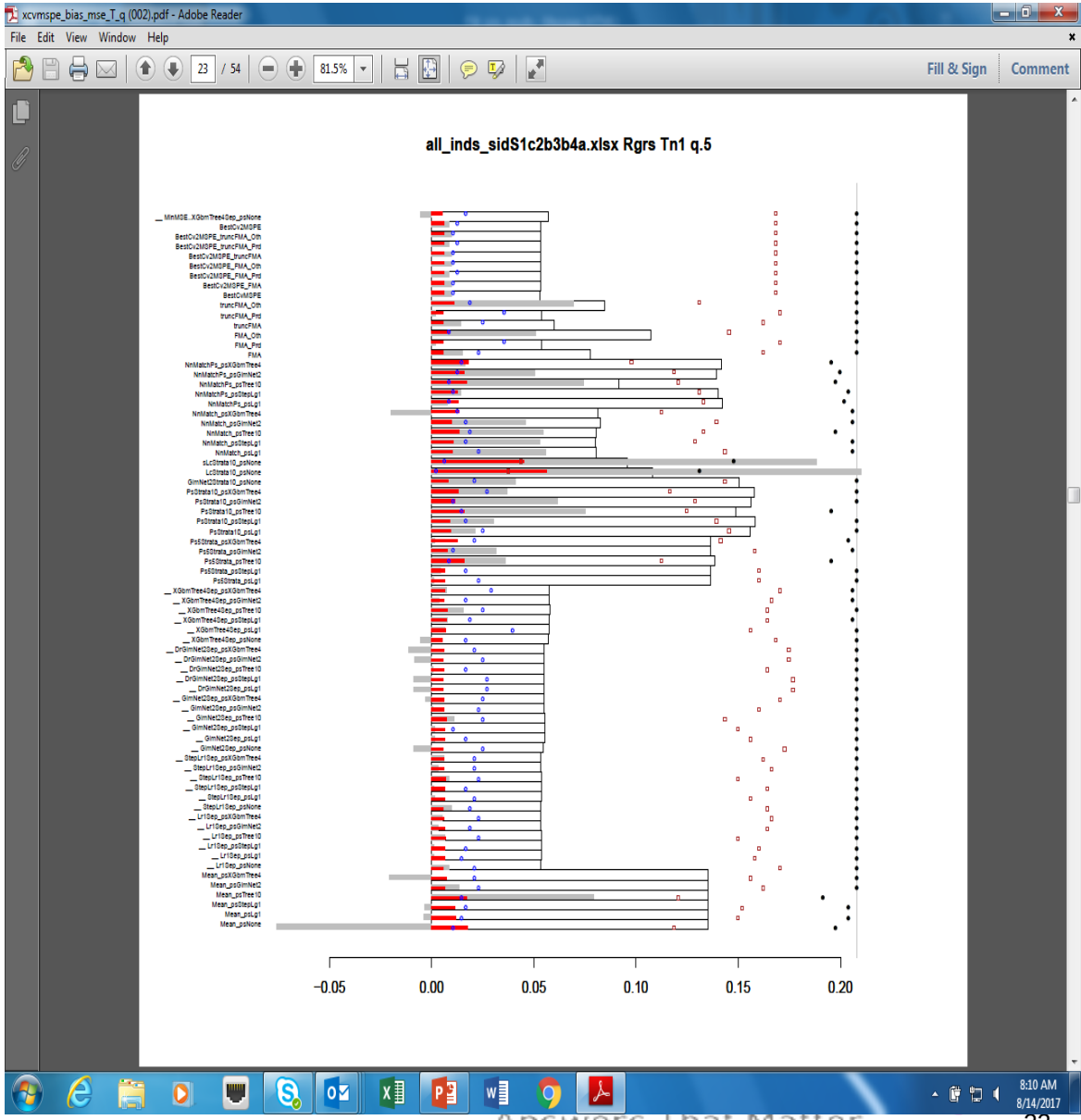
Comparative Effectiveness Simulations

- > 50 methods
- Scenarios based on claims data (Plasmode)

No Gold Standard best method across all scenarios ….. What is best depends upon the data scenario!

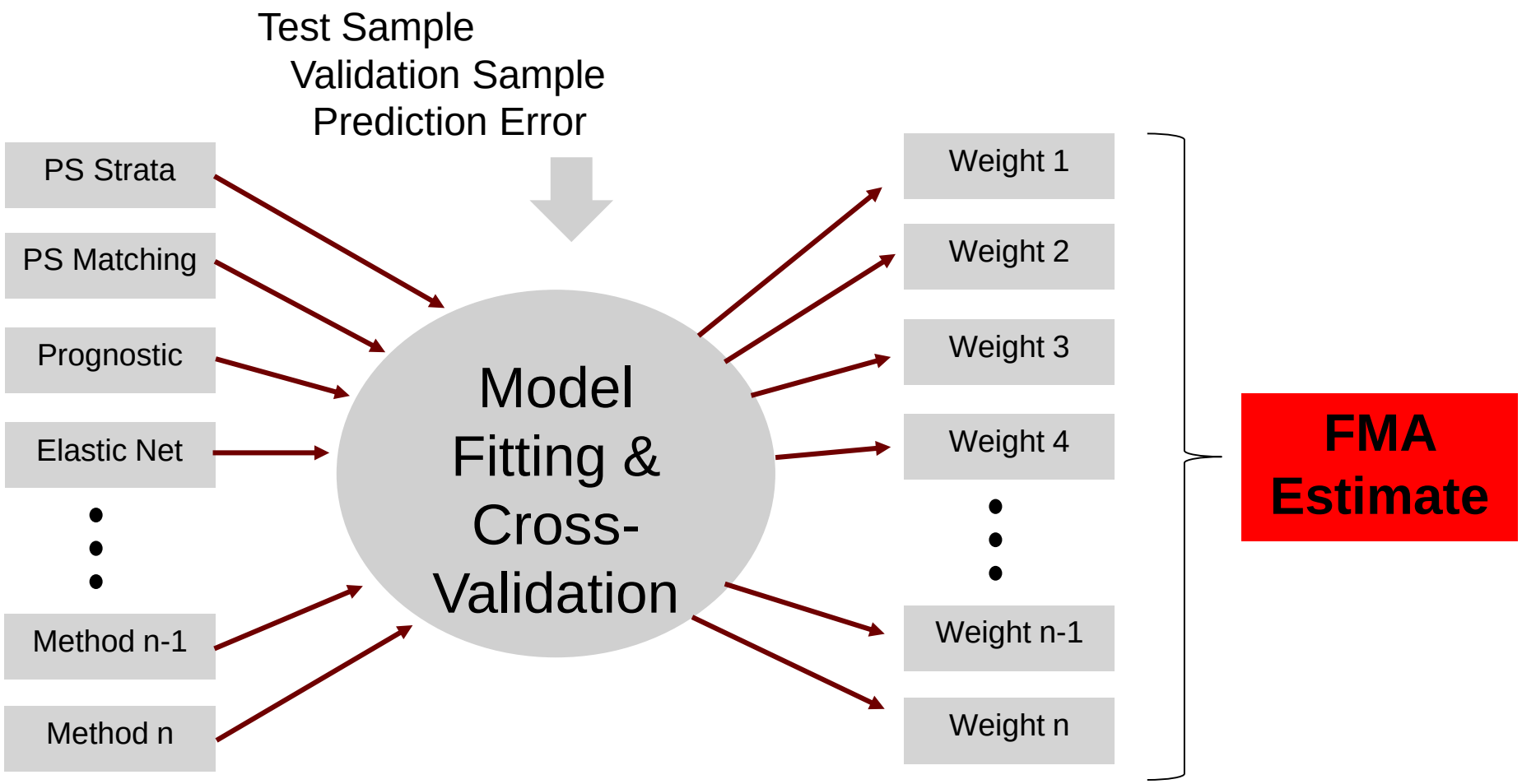
Borrow Ideas from Predictive Modeling:

- Cross Validation / Hold Out
- Model Averaging



Frequentist Model Averaging (FMA)

(Zagar 2017)



Zagar 2017

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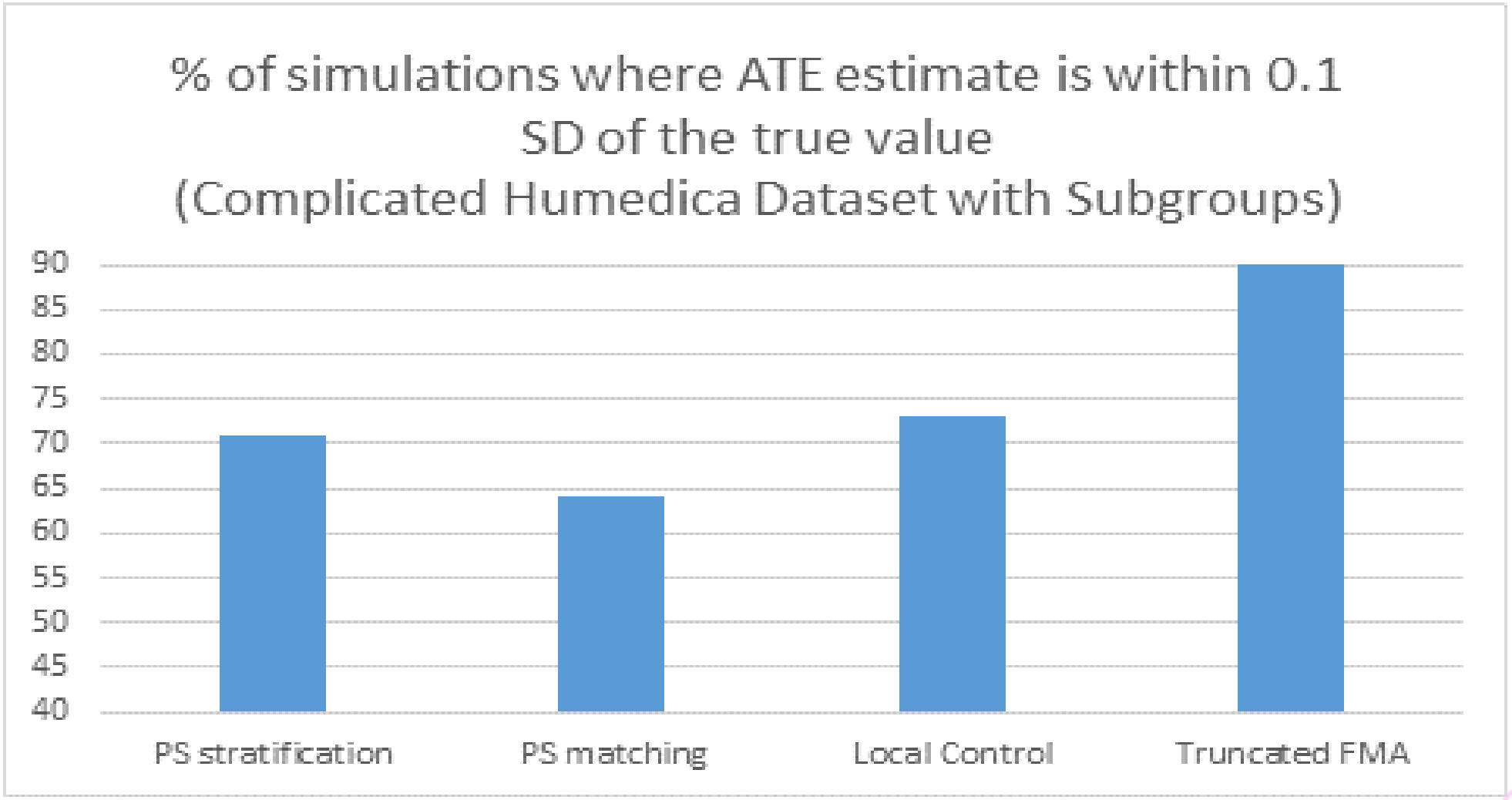
FMA Simulations



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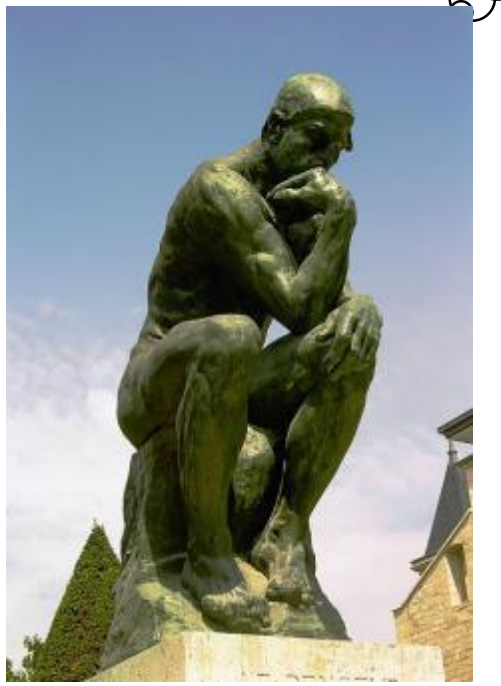
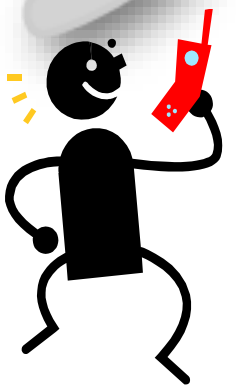
Current State of the Union

What should I do about unmeasured confounding?



Just mention it as a limitation in the Discussion Section and move on!



ORIGINAL REPORT

WILEY

Addressing unmeasured confounding in comparative observational research

Xiang Zhang[1] | Douglas E. Faries[1] | Hu Li[1] | James D. Stamey[2] | Guido W. Imbens[3]

Additional information on Unmeasured Confounder ??

None

- *Plausibility*
  - *Negative control*
  - *Pseudo Trt.*
  - *Partial identification*
  - *Empirical Calibration*
  - *Plausibility Set 1*
- *Adjusted Analysis*
  - *IV*
  - *Difference in differences*
  - *Regression discontinuity*
  - *Missing cause*
  - *Trend-in-trend*
  - *Perturbation variable*

Internal

- *Plausibility*
  - *Plausibility Set 1*
  - *R & R sensitivity*
  - *Rosenbaum Sensitivity*
- *Adjusted Analysis*
  - *Adjusted Analysis set I*
  - *Bayesian Twin Regression*
  - *Multiple imputations*
  - *Propensity calibration*

External

- *Plausibility*
  - *Plausibility Set 1*
  - *R & R sensitivity*
  - *Rosenbaum Sensitivity*
- *Adjusted Analysis*
  - *Bayesian Twin Regression*
  - *Propensity calibration*

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Bayesian Twin Regression Models: Two Stage Model

Outcomes = $\beta_0 + \beta_1 \times cohort$ + $\boldsymbol{\eta} \times$ covariates + $\lambda \times$ UnmConfound

Claims Data

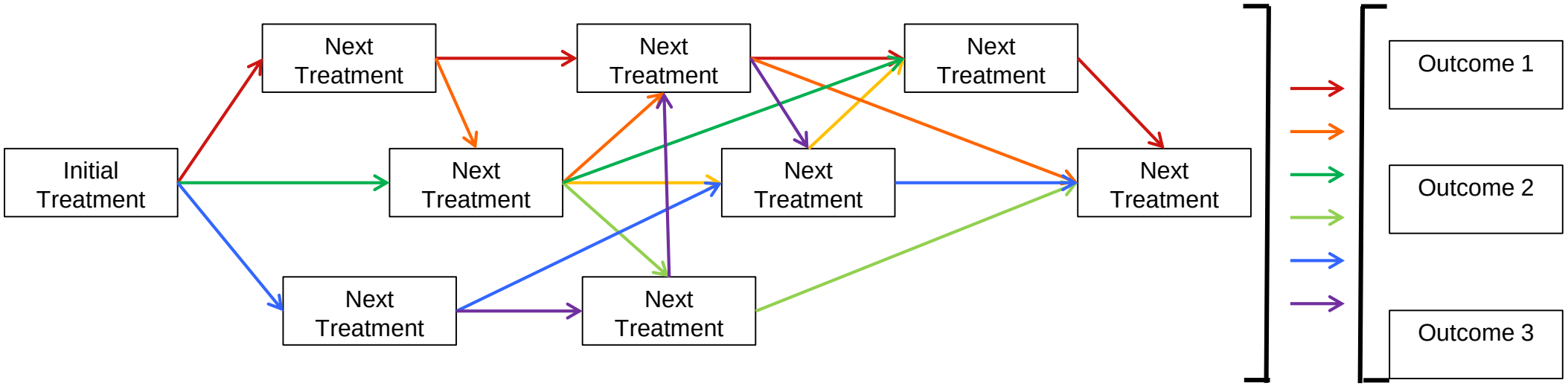
Literature

(2) BMD = $\gamma_0 + \gamma_1 \times cohort$ + $\boldsymbol{\varphi} \times$ covariates

Observ. Study & Public Database

Xiang et al. 2016 PharmacoEpi &Dr S

Can predictive algorithms applied to real world data improve patient outcomes by optimizing individual treatment selection?



Our objective is to find $\mathcal{D}(\cdot)$ to maximize the following value function:

Value function

$$\mathcal{D}_o \in \arg\max_{\mathcal{D}\in R} E^{\mathcal{D}}(Y) = E\left[\frac{I\{A=\mathcal{D}(X)\}}{p(A|X)}Y\right], \quad (1)$$

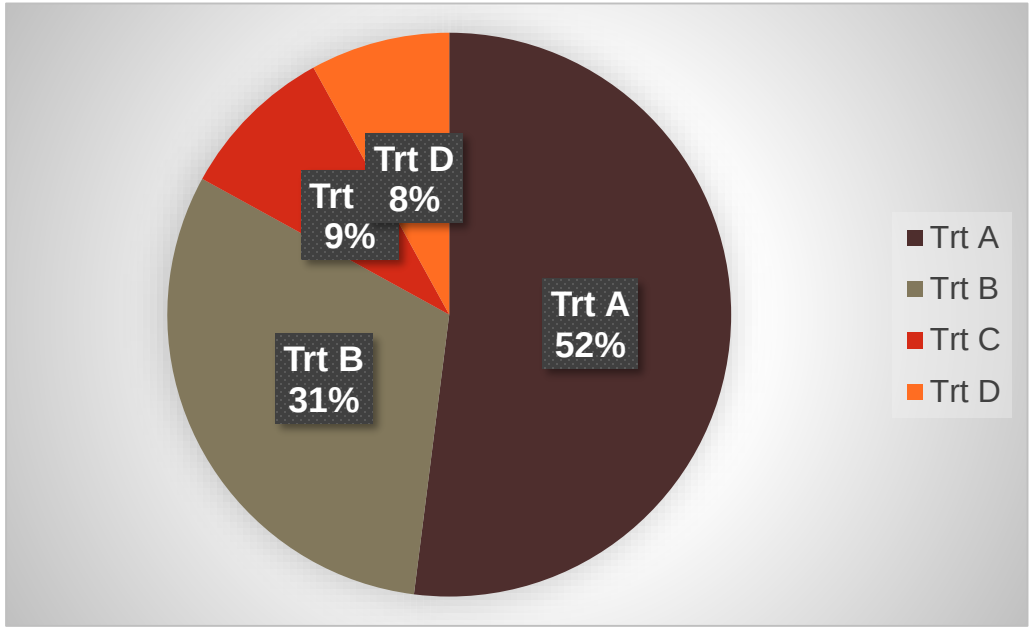
where R is a space of possible treatment recommendations.

(Fu et al. 2016)

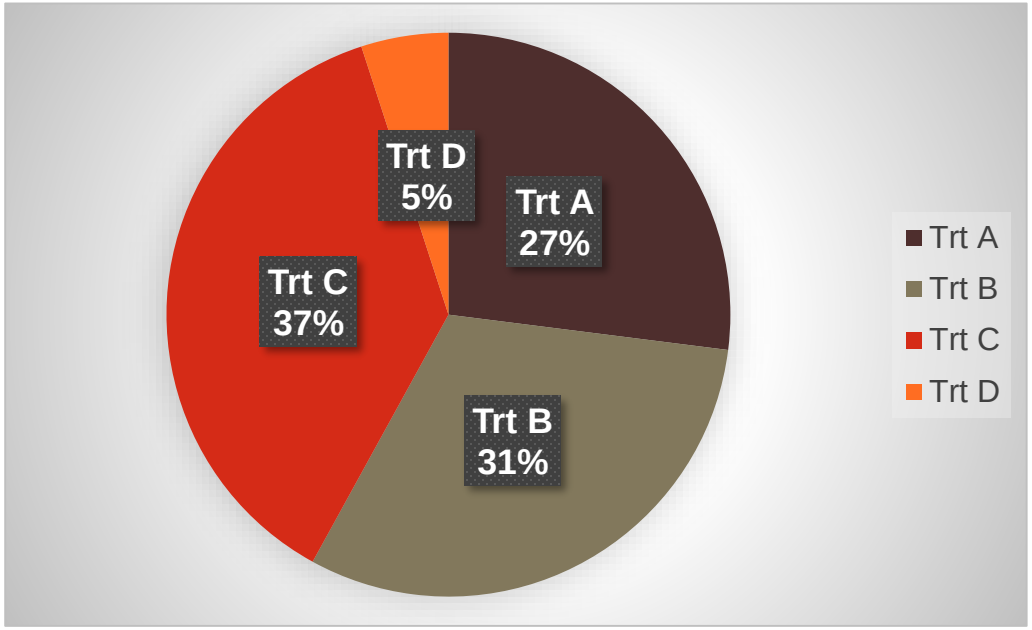
Example Results

Distribution of Treatments & Estimated Gain from ITR

Actual Prescriptions



ML Recommended Prescriptions



ITR Gain of 8.0% in Response* Rate

Observed (Usual Care): 63%

Estimated Using ITR : 71%

Faries et al 2017

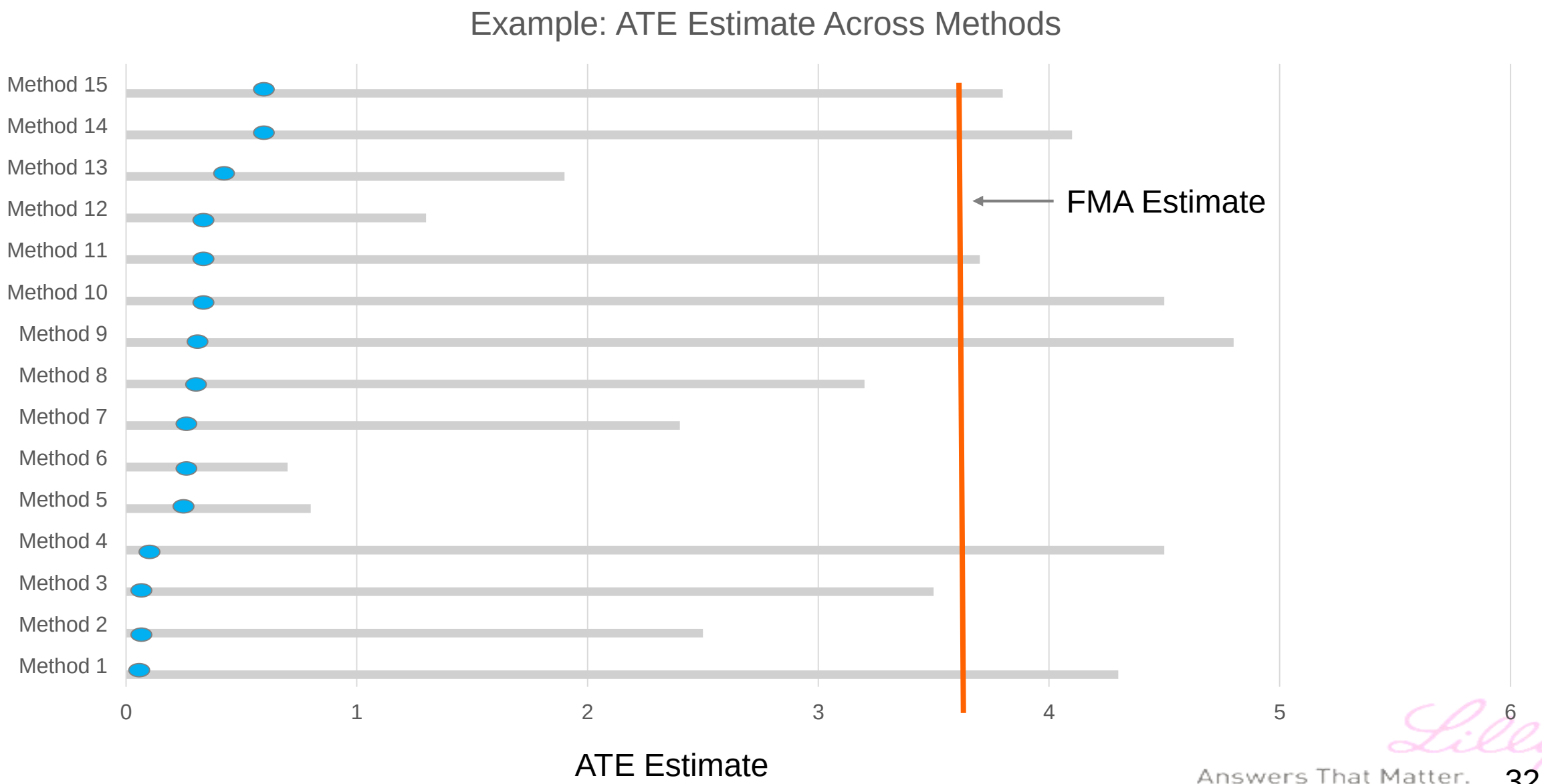
Outline / Conclusion

We need to improve the foundation – the operating characteristics of RWE – to the point where we can have reliable and valid decision making acceptable to regulatory decision makers

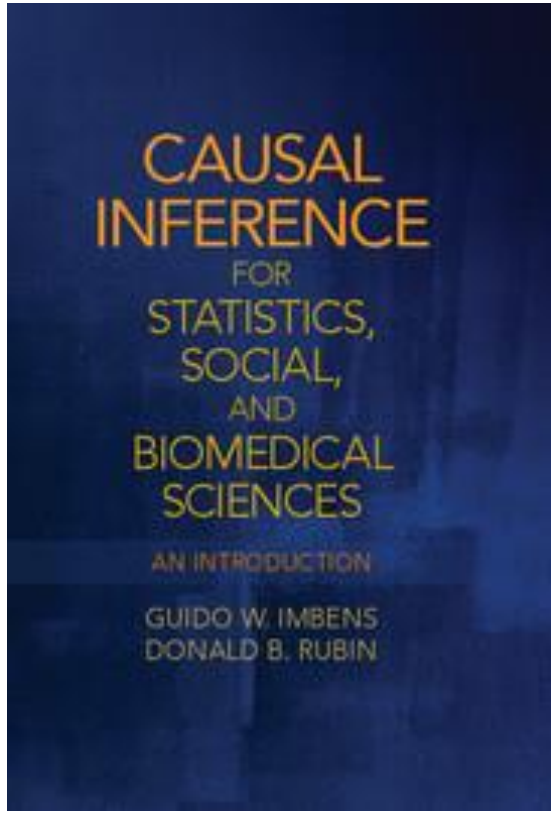
- Re-Assess where we are at: Operating Characteristics
- Design / Data / Analytic Innovations
  - Bias Control
  - Unmeasured Confounding
  - Precision Medicine

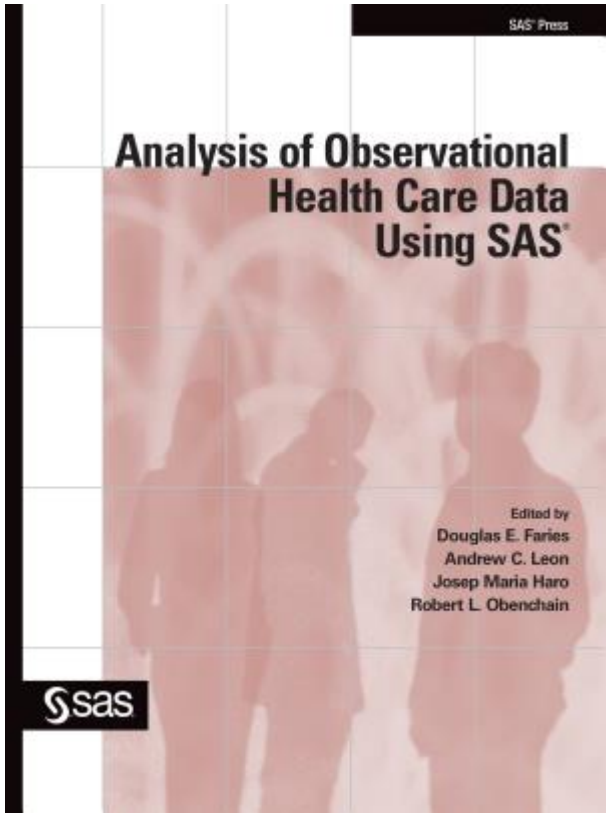
Backups

FMA


Example: ATE Estimate Across Methods
Method 15
Method 14
Method 13
Method 12
Method 11
Method 10
Method 9
Method 8
Method 7
Method 6
Method 5
Method 4
Method 3
Method 2
Method 1
FMA Estimate
0
1
2
3
4
5
6
ATE Estimate

Key References





Causal Inference

Hernán MA, Robins JM (2018)

Chapman & Hall/CRC, forthcoming

Impact of Unmeasured Confounding

Federspiel et al 2016. **Comparing Inverse Probability of Treatment Weighting and Instrumental Variable Methods for the Evaluation of Adenosine Diphosphate Receptor Inhibitors After Percutaneous Coronary Intervention**
JAMA Cardiol. 2016;1(6):655-665. doi:10.1001/jamacardio.2016.1783.

- Instrumental Variables Analysis
  - IVs: site variation and variation over time in intervention use;
  - **Results: MACE HR = 0.68 (0.47, 0.99)**

- Falsification Analyses

Falsification Endpoint		IPTW	IV
Pneumonia		1.31 (0.67, 2.59)	0.22 (0.05, 0.73)
Orthopedic Fracture		2.33 (0.99, 5.53)	0.27 (0.04, 1.45)