Drug Safety Evidence that is Fit For Purpose with National Healthcare Databases

2 March 2017

Sebastian Schneeweiss, MD, ScD
Professor of Medicine and Epidemiology

Division of Pharmacoepidemiology and Pharmacoeconomics,
Dept of Medicine, Brigham & Women's Hospital/ Harvard Medical School

SOUNDING BOARD

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.

SOUNDING BOARD

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. Eindman, 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.

SOUNDING BOARD

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., Robert Temple, M.D., Ja

Drug safety assessment
- Presence and magnitude of harm
- Subgroups with acceptable benefit/harm

Drug utilization monitoring
- Frequency and duration of new use
- Use within and outside of indication

Adaptive Biomedical Innovation
- From biomarkers to clinical endpoints
- Broadening initial indications

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.

Safety Example:

Database Study → *followed by* → **RCT**

The NEW ENGLAND JOURNAL of MEDICINE — FEBRUARY 21, 2008

Aprotinin during Coronary-Artery Bypass Grafting and Risk of Death

Sebastian Schneeweiss, M.D., Sc.D., John D. Seeger, Pharm.D., Dr.P.H., Joan Landon, M.P.H., and Alexander M. Walker, M.D., Dr.P.H.

The NEW ENGLAND JOURNAL of MEDICINE — MAY 29, 2008

A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery

Dean A. Fergusson, M.H.A., Ph.D., Paul C. Hébert, M.D., M.H.Sc., C. David Mazer, M.D., Stephen Fremes, M.D., Charles MacAdams, M.D., John M. Murkin, M.D., Kevin Teoh, M.D., M.Sc., Peter C. Duke, M.D., Ramiro Arellano, M.D., M.Sc., Morris A. Blajchman, M.D., Jean S. Bussières, M.D., Dany Côté, M.D., Jacek Karski, M.D., Raymond Martineau, M.D.,* James A. Robbee, M.D., M.B.A., Marc Rodger, M.D., M.Sc., George Wells, Ph.D., Jennifer Clinch, M.A., and Roanda Pretorius, M.Sc., for the BART Investigators†

Safety Example:

Database Study → *followed by* → **RCT**

The NEW ENGLAND JOURNAL of MEDICINE — FEBRUARY 21, 2008

Aprotinin during Coronary-Artery Bypass Grafting and Risk of Death

Sebastian Schneeweiss, M.D., Sc.D., John D. Seeger, Pharm.D., Dr.P.H., Joan Landon, M.P.H., and Alexander M. Walker, M.D., Dr.P.H.

The NEW ENGLAND JOURNAL of MEDICINE — MAY 29, 2008

A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery

Dean A. Fergusson, M.H.A., Ph.D., Paul C. Hébert, M.D., M.H.Sc., C. David Mazer, M.D., Stephen Fremes, M.D., Charles MacAdams, M.D., John M. Murkin, M.D., Kevin Teoh, M.D., M.Sc., Peter C. Duke, M.D., Ramiro Arellano, M.D., M.Sc., Morris A. Blajchman, M.D., Jean S. Bussières, M.D., Dany Côté, M.D., Jacek Karski, M.D., Raymond Martineau, M.D.,* James A. Robbee, M.D., M.B.A., Marc Rodger, M.D., M.Sc., George Wells, Ph.D., Jennifer Clinch, M.A., and Roanda Pretorius, M.Sc., for the BART Investigators†

Effectiveness Example:

RCT → *followed by* → **Database Study**

The NEW ENGLAND JOURNAL of MEDICINE — SEPTEMBER 17, 2009

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.B., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

Circulation

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Shea, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houstoun, PhamD, MPH; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

Safety Example:

Database Study → *followed by* → **RCT**

The NEW ENGLAND JOURNAL of MEDICINE — FEBRUARY 21, 2008

Aprotinin during Coronary-Artery Bypass Grafting and Risk of Death

Sebastian Schneeweiss, M.D., Sc.D., John D. Seeger, Pharm.D., Dr.P.H., Joan Landon, M.P.H., and Alexander M. Walker, M.D., Dr.P.H.

The NEW ENGLAND JOURNAL of MEDICINE — MAY 29, 2008

A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery

Dean A. Fergusson, M.H.A., Ph.D., Paul C. Hébert, M.D., M.H.Sc., C. David Mazer, M.D., Stephen Fremes, M.D., Charles MacAdams, M.D., John M. Murkin, M.D., Kevin Teoh, M.D., M.Sc., Peter C. Duke, M.D., Ramiro Arellano, M.D., M.Sc., Morris A. Blajchman, M.D., Jean S. Bussières, M.D., Dany Côté, M.D., Jacek Karski, M.D., Raymond Martineau, M.D.,* James A. Robbee, M.D., M.B.A., Marc Rodger, M.D., M.Sc., George Wells, Ph.D., Jennifer Clinch, M.A., and Roanda Pretorius, M.Sc., for the BART Investigators†

Why did these database studies get it right?

Effect

The NEW ENGLAND JOURNAL of MEDICINE — SEPTEMBER 17, 2009

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.B., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

Circulation

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Shea, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houstoun, PhamD, MPH; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

Safety Example:

Database Study *followed by* **RCT**


The NEW ENGLAND JOURNAL of MEDICINE

Aprotinin during Coronary-Artery Bypass Grafting and Risk of Death

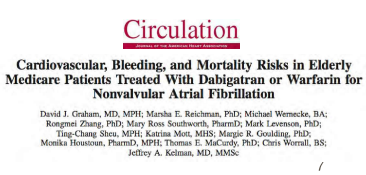

The NEW ENGLAND JOURNAL of MEDICINE

A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery

How confident that the **next study will get it right**?

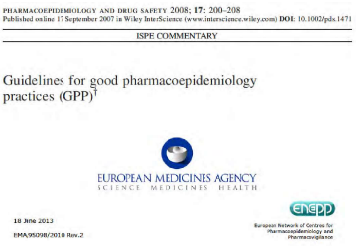

The NEW ENGLAND JOURNAL of MEDICINE

Dabigatran versus Warfarin in Patients with Atrial Fibrillation


Circulation

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

Guidelines to build Confidence in Database Studies


PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2008; 17: 200–208

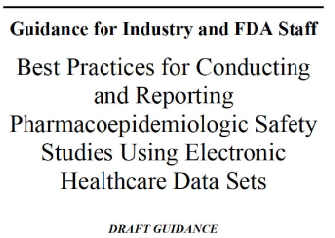
ISPE COMMENTARY

Guidelines for good pharmacoepidemiology practices (GPP)†

EUROPEAN MEDICINES AGENCY

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP

Guide on Methodological Standards in Pharmacoepidemiology (Revision 2)


Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets

DRAFT GUIDANCE


GRACE Principles: Recognizing High-Quality Observational Studies of Comparative Effectiveness

8

Decision-relevant Evidence: The right evidence is generated the right way at the right time

1) Meaningful evidence
2) Valid evidence
3) Expedited evidence
4) Transparent evidence


Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making

S Schneeweiss[1], H-G Eichler[2], A Garcia-Altes[3], C Chinn[4], A-V Eggimann[5], S Garner[6], W Goettsch[7], R Lim[8], W Löbker[9], D Martin[10], T Müller[11], BJ Park[12], R Platt[13], S Priddy[14], M Ruhl[15], A Spooner[16], B Vannieuwenhuyse[17] and RJ Willke[18]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 100 NUMBER 6 | DECEMBER 2016

9

1) Meaningful evidence
2) Valid evidence
3) Expedited evidence
4) Transparent evidence

- **Data Quality**
  - Fit for purpose
- **Data Flexibility**
  - Match data type to the question
- **Meaningful statistics**
  - Metrics that matter

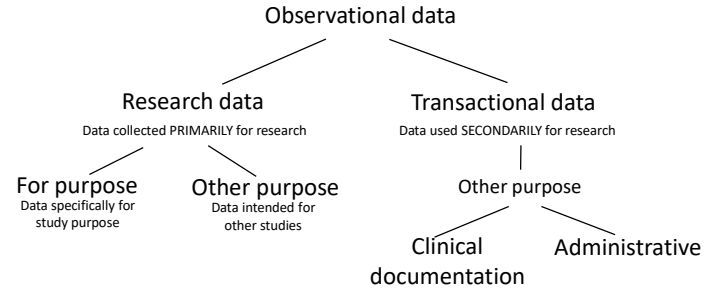
10

Data quality: Fit for purpose

- **Accurate assessment of Exposure:**
  - Completeness of repeated uses
  - Prescribing vs. dispensing vs. use of drugs
- **Accurate assessment of Outcome:**
  - High specificity of outcome assessment when estimating relative effect measures: risk ratio, rate ratio, hazard ratio
  - Reasonable sensitivity to preserve event counts
- **Complete assessment of Confounders:**
  - Reduced unobserved confounding
  - Pre-exposure measurement, avoid adjustment for intermediates

11

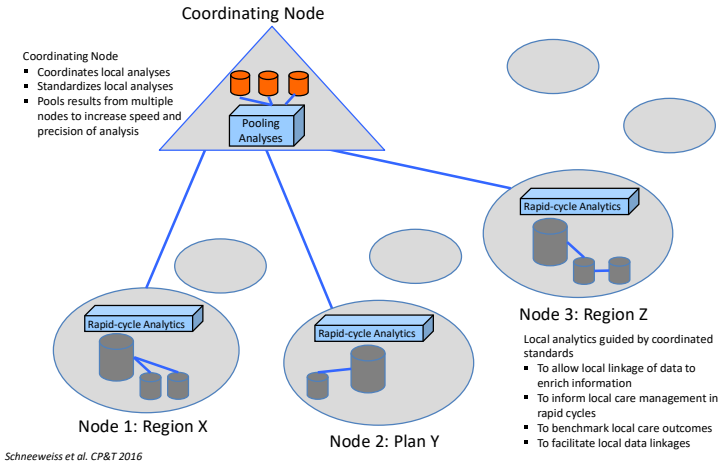
Data quality: Fit for purpose



Example	▪ Framingham Study ▪ Cardiovas Health Study ▪ Slone Birth Defects Study ▪ *Some registries*	▪ Nurses' Health Study 1 ▪ *Some registries*	▪ EHR-based studies ▪ NDI linkage ▪ Lab test databases ▪ *Some registries*	▪ Claims data studies ▪ Geocoding/census
E				
O				
C				

12

Data flexibility: Match data type to the question



Schneeweiss et al. CP&T 2016

Basic epidemiologic measures are key!

- Counts of users
- Duration of use
- Population at risk
- Incidence rates of events

Sentinel

Table 1a: Summary of Incident Influenza Antiviral Drug Use among Patients with Medical and Drug Coverage in the Sentinel Distributed Database between January 1, 2010 and December 31, 2015, by Drug and Washout Period

	New Users	New Episodes	Dispensings	Days Supplied	Amount Supplied	Years at Risk	Eligible Members	Member-Years	New Users / 1K Eligible Members	Days Supplied/ User	Dispensings / User	DaysSupplied/ Dispensing
Incident Use of Oseltamivir Capsules (5 day washout)												
	1,978,276	2,102,885	2,114,557	12,062,113	23,524,293	33,082.7	101,947,808	119,957,555.4	19.40	6.1	1.07	5.70
Incident Use of Oseltamivir Capsules (90 day washout)												
	1,975,692	2,090,667	2,102,055	11,985,963	23,367,554	32,872.2	101,934,600	119,595,694.0	19.38	6.0	1.06	5.70
Incident Use of Oseltamivir Powder (45 day washout)												
	459,758	494,188	496,763	3,178,893	44,274,001	8,713.7	101,947,808	119,957,555.4	4.51	6.9	1.08	6.40

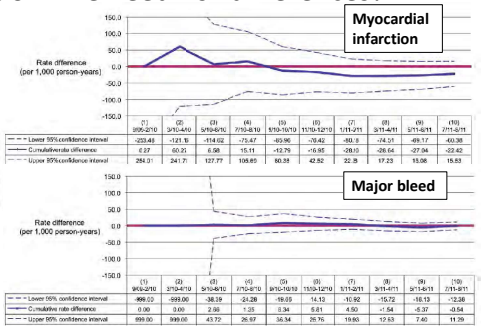
Table 4c. Summary of Incident Dabigatran and Warfarin Use and GIH or ICH Events in the MSDD between October 19, 2010 and December 31, 2011, by Drug, Incidence Criteria, and Washout Period

	New Users	Dispensings	Total Days Supplied	Days at Risk	New GIH or ICH Events	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Dispensings/ User	Days Supplied/ User	Days Supplied/ Dispensing	New GIH or ICH Events/100k Days at Risk
Dabigatran												
Incident with respect to Dabigatran												
183-Day Washout												
2010	2,925	11,742	411,745	456,574	11	30,069,142	2,117,614,876	0.1	4.0	151.0	37.6	2.4
2011	21,922	59,053	2,130,419	2,303,321	67	31,468,879	8,862,407,779	0.7	2.7	101.7	37.8	2.9
365-Day Washout												
2010	2,567	10,325	390,096	403,495	10	24,987,931	1,802,499,608	0.1	4.0	152.0	37.8	2.5
2011	20,254	55,255	2,094,130	2,166,806	60	26,456,599	7,794,953,420	0.8	2.7	103.4	37.9	2.8

Net benefit calculation: We need risk differences!

Exposures:
Clopidogrel vs. prasogrel

Outcomes:
Benefit: MI prevention
Harm: Major bleed



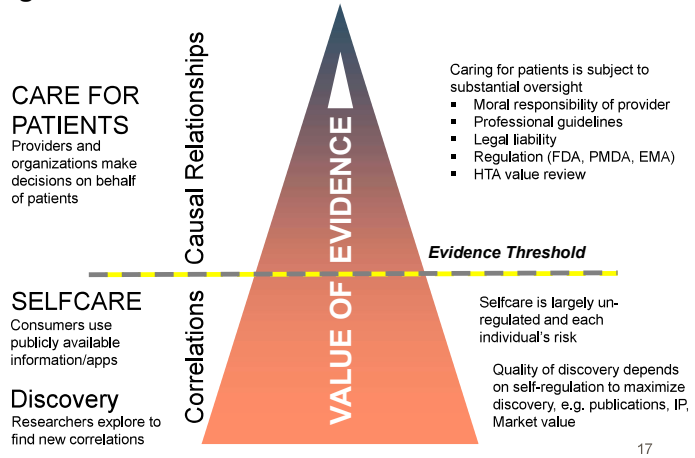
Report Risk Differences

Gagne et al. Drug Saf 2014

1) Meaningful evidence
2) Valid evidence
3) Expedited evidence
4) Transparent evidence

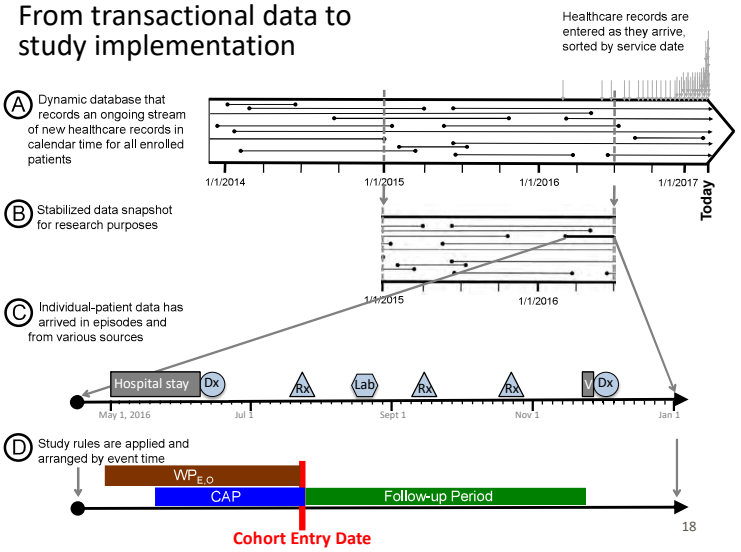
- **Avoid design flaws**
  - Think of target trial
- **Approach confounding in context**
  - Question & Data type dictate approach
- **Reduce investigator error**
  - Structured approaches

Most Healthcare Decisions Need To Be Based On Insights Above A Critical Evidence Threshold

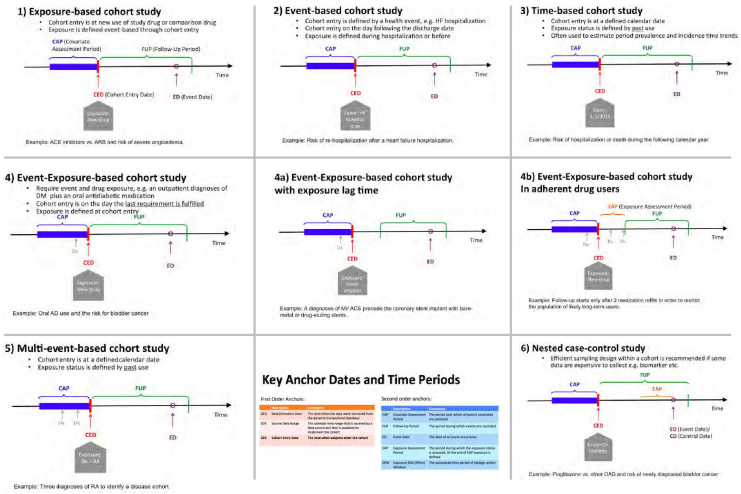


Schneeweiss CPT 2016

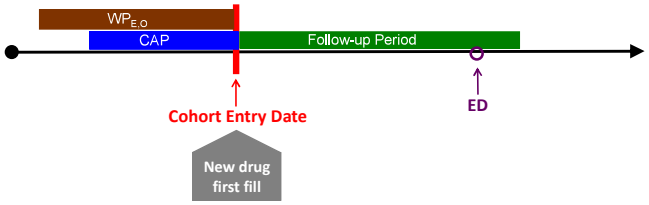
From transactional data to study implementation



The many ways to implement a cohort study



Clarity in implementation reduces massive flaws

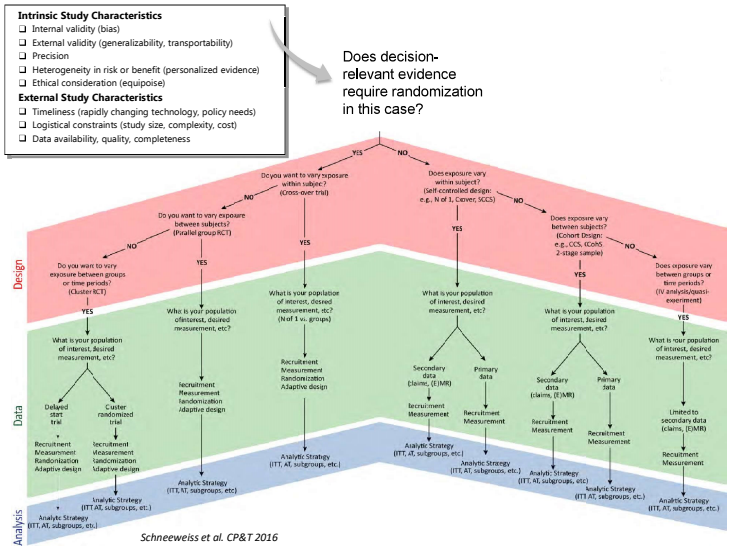


Avoidable design flaws:

Study design flaws = substantial bias

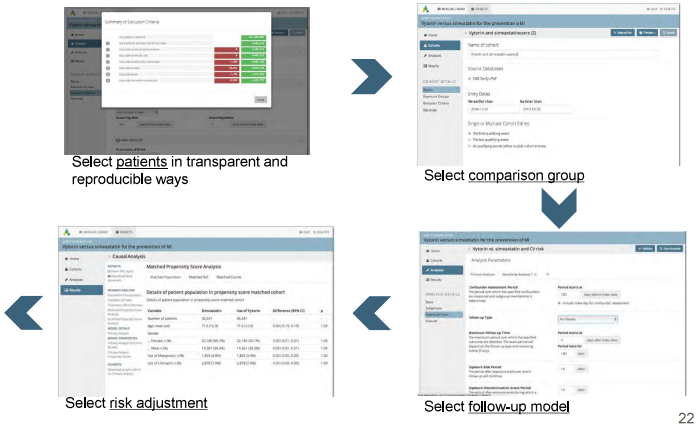
- Reverse Causation
- Immortal time bias
- Adjustment for causal intermediates
- Depletion of susceptible
- Unobservable time bias

20

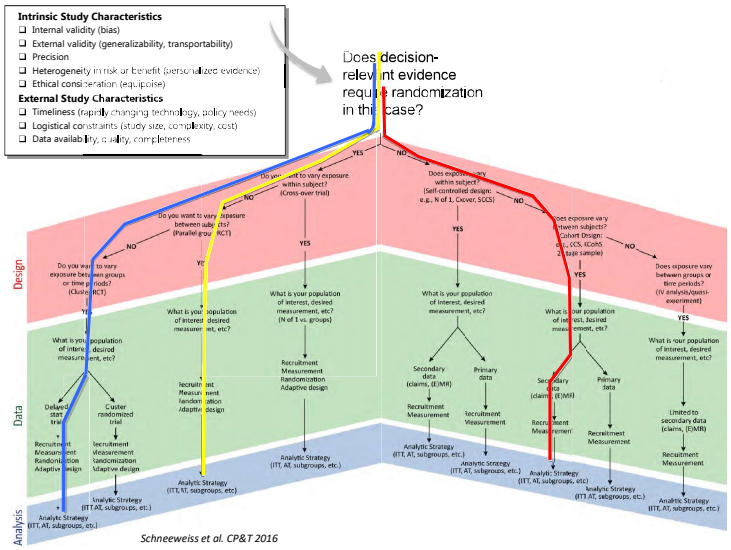


Schneeweiss et al. CP&T 2016

User guidance reduces investigator error

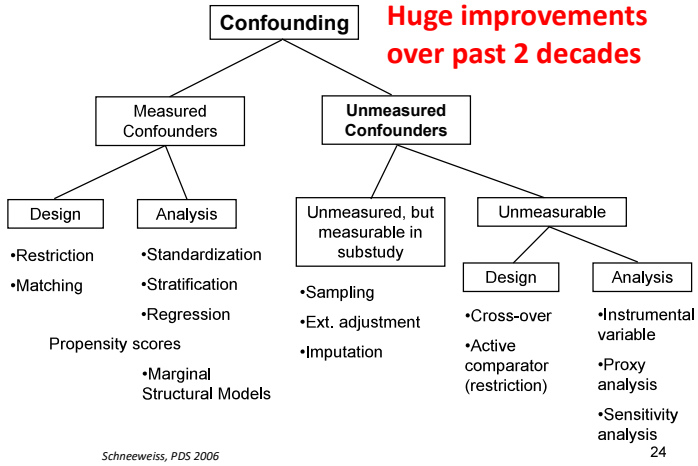


22



Schneeweiss et al. CP&T 2016

Dealing with Confounding



Schneeweiss, PDS 2006

24

Why we like propensity score matching

Propensity scores:

- **Few outcomes**
- **Many covariates**

Primary data collection	**Database Studies**
▪ Precisely identified covariates	▪ Known constructs of covariates
▪ Well-defined measurement	▪ **No control of covariate measurement**
▪ A small number of selected covariates	▪ **Large numbers of covariates can be generated**

Matching:

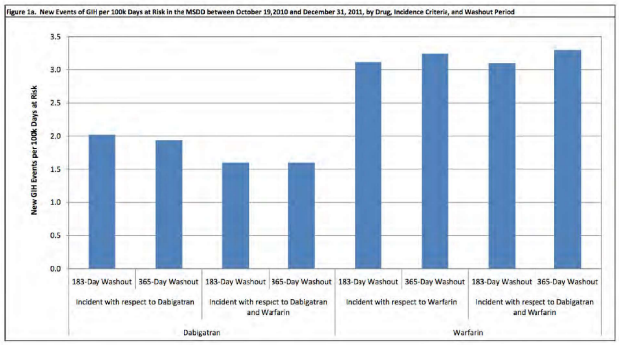
- **Transparency** in the achieved balance
- Trimming of subjects that cannot be matched (areas of no support)

Schneeweiss, Rassen et al. Epidemiol 2009;
Rassen et al. Am J Epidemiol 2014

Sensitivity analyses

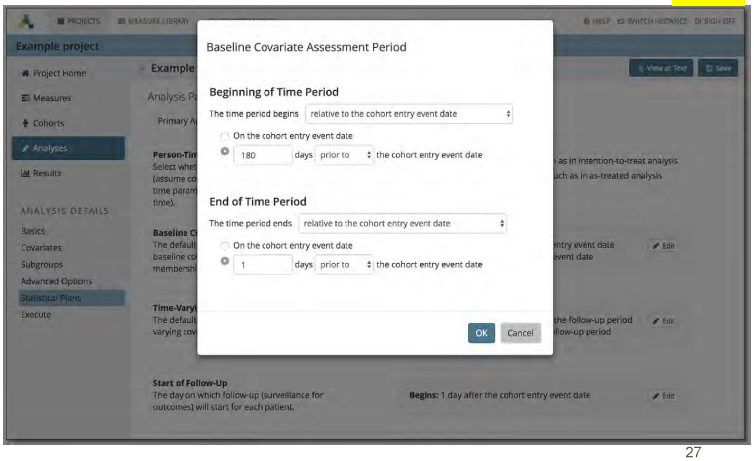
FDA likes to see sensitivity analyses to check the robustness of findings
However, rarely done because too labor-intensive

Mini-Sentinel



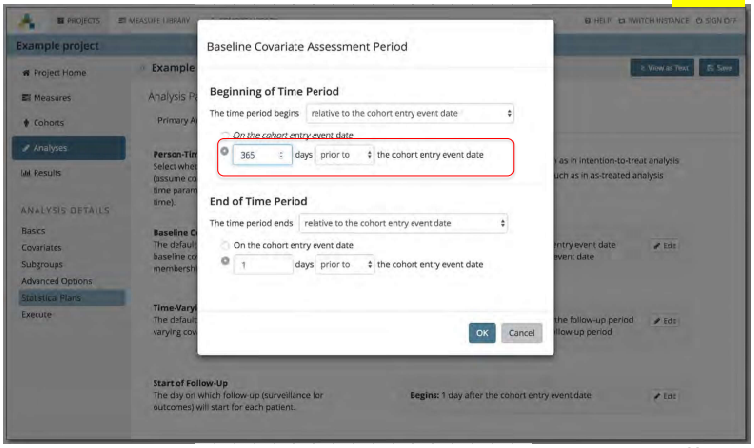
Sensitivity analyses with a validated platform

CAP



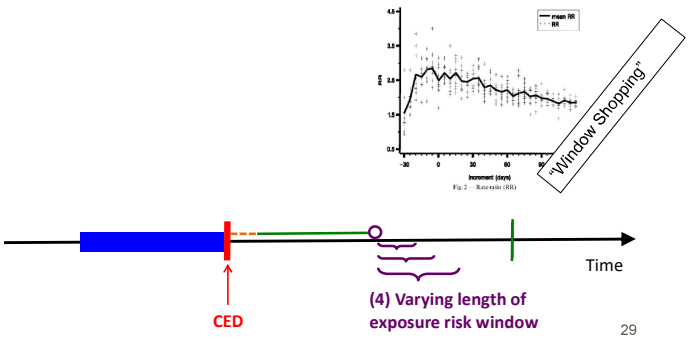
Sensitivity analyses with a validated platform

CAP



Misspecified Exposure Risk Window

- The ERW is shorter than the biologic effect or too long
- The ERW may or may not overlap with a grace period
- Sensitivity analysis:
  - Shorten and lengthen ERW

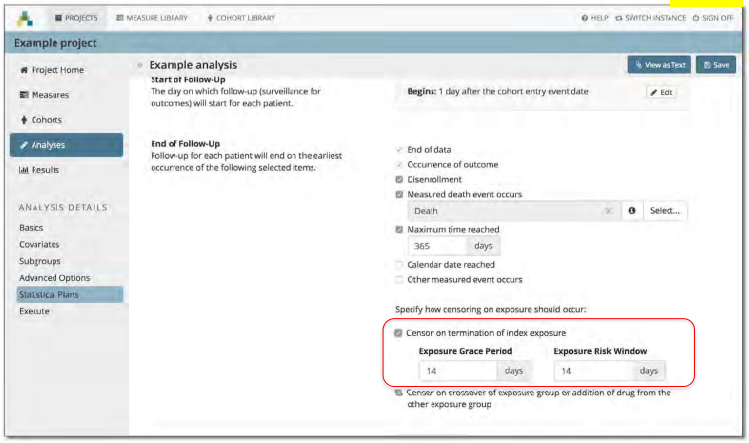


Schneeweiss S & Avorn J, JClinEpi 2005

MacMahon AD et al., PDS 1998

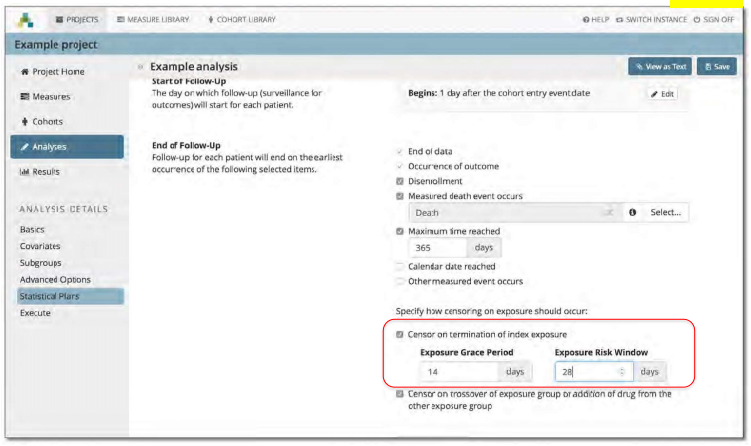
Sensitivity analyses with a validated platform

ERW



Sensitivity analyses with a validated platform

ERW



Sensitivity analyses help build confidence

ARTHRITIS & RHEUMATISM
Vol. 56, No. 6, June 2007, pp 1754–1764
DOI 10.1002/art.22600
© 2007, American College of Rheumatology

Anti–Tumor Necrosis Factor α Therapy and the Risk of Serious Bacterial Infections in Elderly Patients With Rheumatoid Arthritis

Sebastian Schneeweiss, Soko Setoguchi, Michael E. Weinblatt, Jeffrey N. Katz, Jerry Avorn, Paul E. Sax, Raisa Levin, and Daniel H. Solomon

Sensitivity analyses help build confidence

ARTHRITIS & RHEUMATISM
Vol. 56, No. 6, June 2007, pp 1754–1764
DOI 10.1002/art.22600
© 2007, American College of Rheumatology

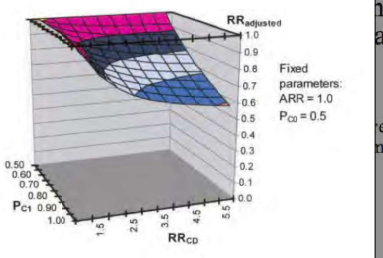
Anti–Tu… Seriou… …nd the Risk of …atients With

Sebastian Schne… …ey N. Katz, Jerry Avorn, …non

APPENDIX A: QUANTITATIVE SENSITIVITY ANALYSIS OF RESIDUAL CONFOUNDING

We performed a sensitivity analysis of residual confounding as a function of the association of RA disease severity with anti-TNFα therapy and as a function of the association of RA disease severity with increased rates of infection. We used the following definitions (30) and applied the assumptions described:

ARR represents the apparent, or observed, relative risk of anti-TNFα use. Our study found an ARR of 1.0. For rare outcomes, we can assume that the relative risk estimate closely approximates the rate ratio.



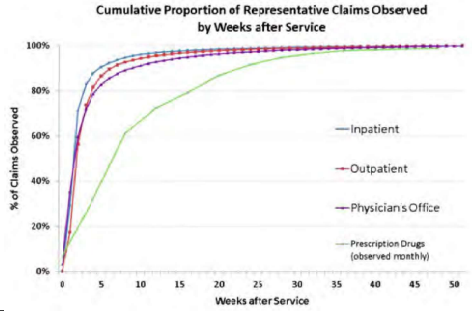
1) Meaningful evidence
2) Valid evidence
3) Expedited evidence
4) Transparent evidence

- **Speed through closeness to data**
  - Being embedded in the data stream
- **Speed through data standards**
  - Sentinel common data model
- **Speed through analytic tools**
  - Speed without compromising science

How can we optimize validity at high speed across multiple data systems?

Utilizing Medicare claims data for real-time drug safety evaluations: is it feasible?†,‡

Abraham G. Hartzema[1]*, Judith A. Racoosin[2], Thomas E. MaCurdy[3,4], Jonathan M. Gibbs[4] and Jeffrey A. Kelman[5]

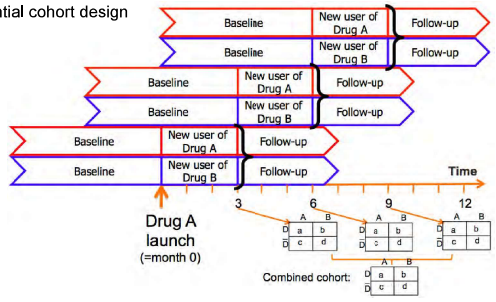


Rapid-cycle analytics without compromising validity across multiple data systems

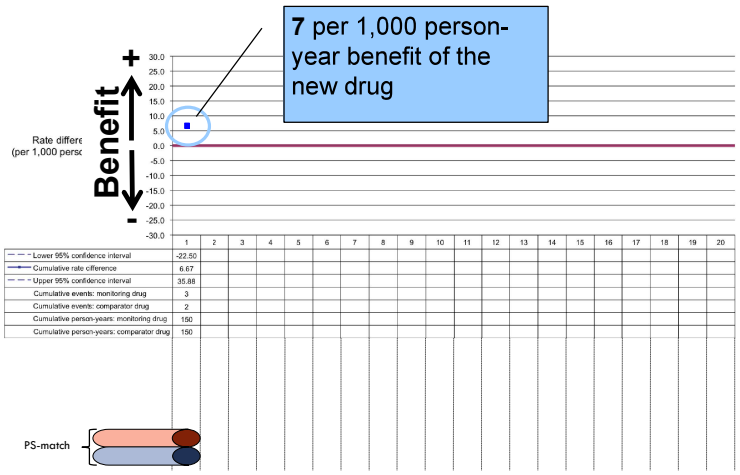
Assessing the Comparative Effectiveness of Newly Marketed Medications: Methodological Challenges and Implications for Drug Development

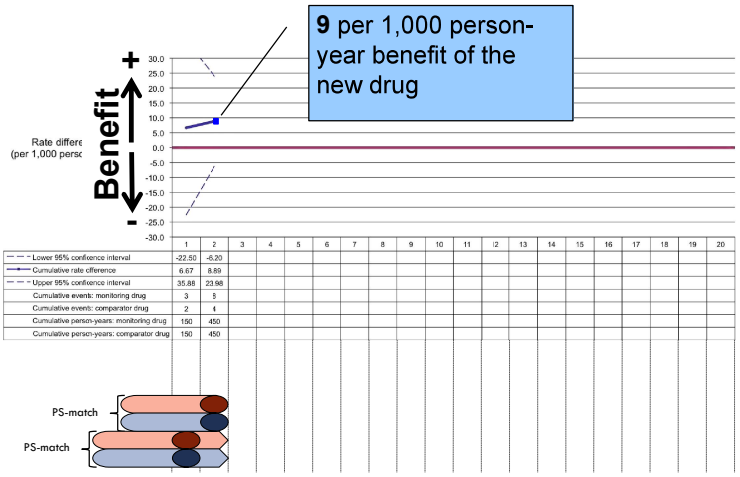
S Schneeweiss[1], JJ Gagne[1], RJ Glynn[1], M Ruhl[2] and JA Rasser[1]

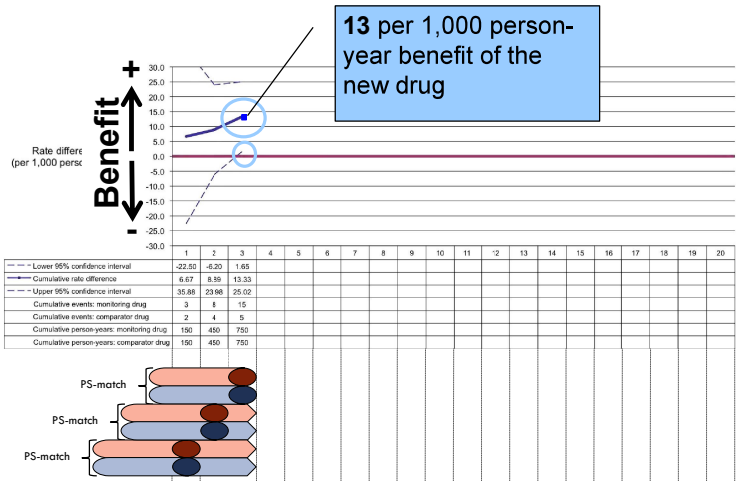
Sequential cohort design

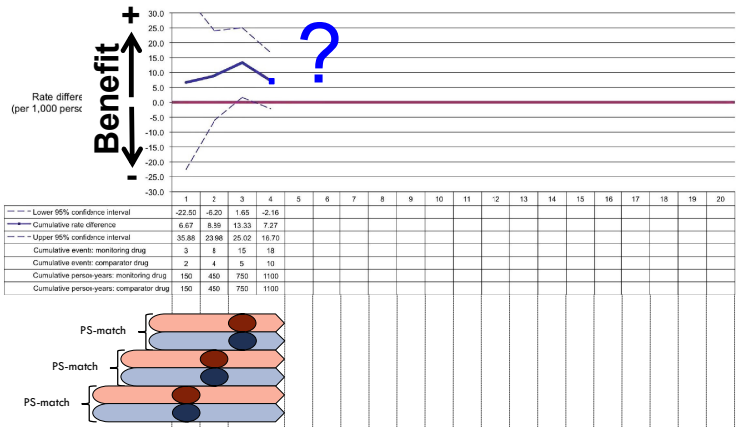


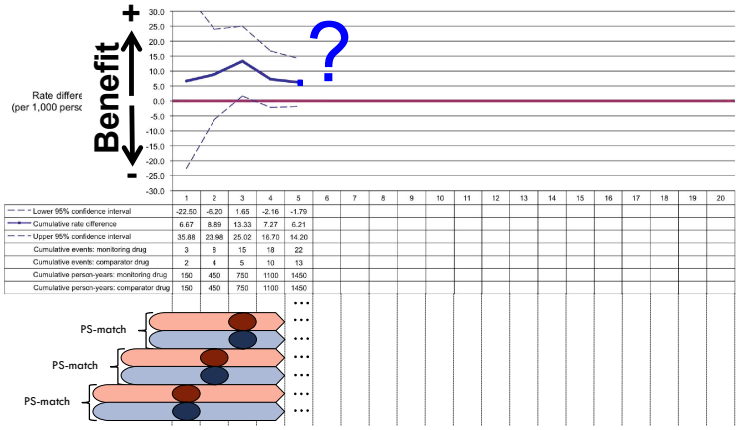
When is a benefit real?

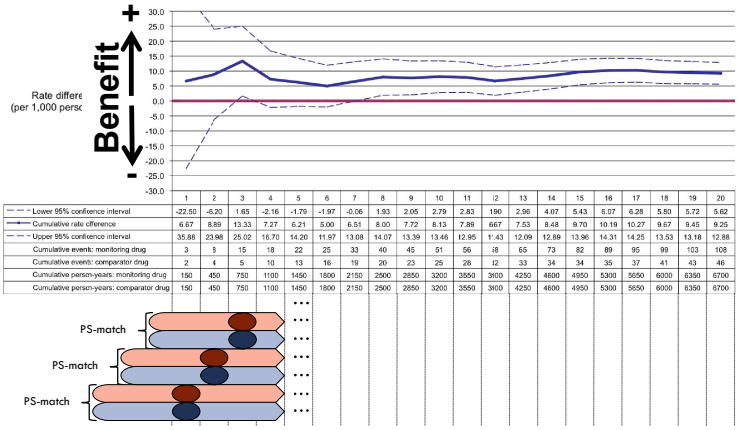




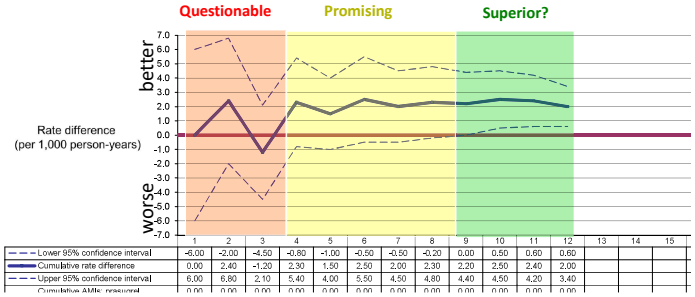








Decision making in a monitoring system



Questionable:
- Investigate subgroup effects
- Continue evaluation

Promising:
- Continue program
- Continue evaluation
- Moderately expand program

Superior:
- Widely disseminate

Schneeweiss, Shrank, Ruhl, Maclure, IJTAHC 2015

1) **Meaningful evidence**
2) **Valid evidence**
3) **Expedited evidence**
4) **Transparent evidence**

- **Transparency -> Reproducibility**
  - Be able to reproduce in same data
- **Shared analytics & auditability**
  - Withstand detailed audits of past data
- **Accepted statistical procedure**
  - We have plenty statistical tools

Transparency and Reproducibility of Observational Cohort Studies Using Large Healthcare Databases.

SV Wang[1], P Verpillat[2], JA Rassen[3], A Patrick[3], EM Garry[3] and DB Bartels[2,5]

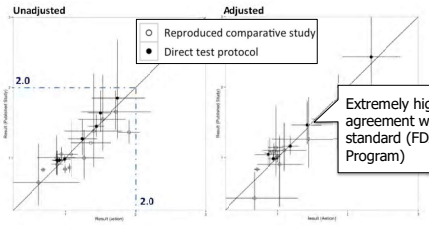
CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 99 NUMBER 3 | MARCH 2016

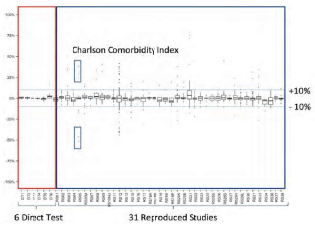
Reasons for Limited Reproducibility

52% of reproduced studies had inadequate reporting in one or more areas:

1. Code lists/algorithms not reported
2. Covariate assessment period not reported
3. Follow up period not reported
4. Unclear which baseline characteristics included in adjusted models or propensity scores

Scientific validation of a platform against FDA standard





Wang S. et al. CP&T 2016:

Aetion is the only fully validated platform for healthcare database analytics

Kim S. et al. A&R in press:

FDA post-marketing commitment of a multi-DB cardiovascular safety study

Fralick M. et al. Ann Int Med in press:

Risk of ketoacidosis after commencing SGLT-2 inhibitors

Patorno E. et al. in progress:

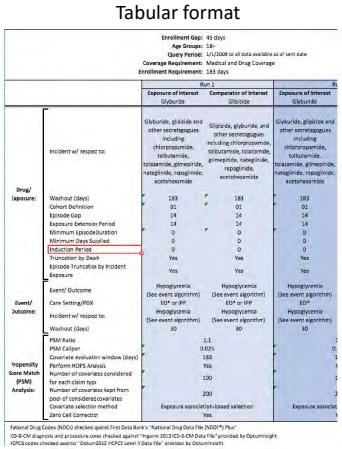
SGLT-2 inhibitor safety/effect. surveillance program for EMA

>10,000 analyses
by 15 organizations
(Pharma, payer, academia, EMA)

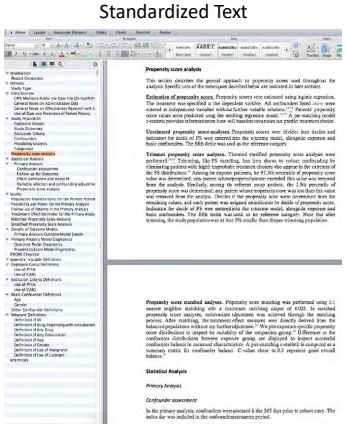
CONFIDENTIAL

Analytic tools are build for transparency

Tabular format



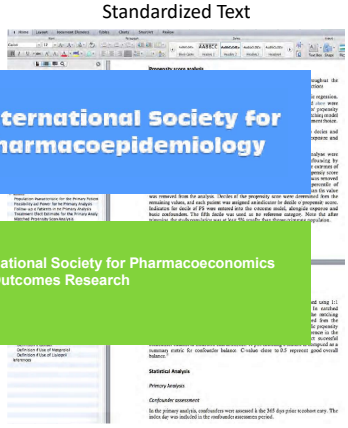
Standardized Text



Analytic tools are build for transparency

Tabular format

Standardized Text



Depositing codes for reproducibility

OPEN ACCESS Freely available online PLOS ONE

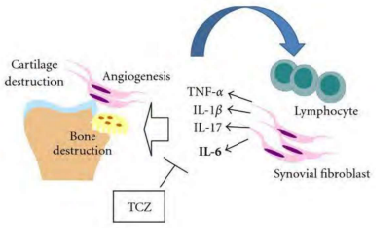
ClinicalCodes: An Online Clinical Codes Repository to Improve the Validity and Reproducibility of Research Using Electronic Medical Records

David A. Springate[1,2*], Evangelos Kontopantelis[1,3], Darren M. Ashcroft[4], Ivan Olier[5], Rosa Parisi[6], Edmore Chamapiwa[1], David Reeves[1,2]

49

Case study: TCZ

- Tocilizumab (TCZ) inhibits the IL-6 receptor
- TCZ was approved by the FDA in 2010 for treatment of rheumatoid arthritis
- Early studies showed an increase in LDL and triglycerides
- FDA wanted to ensure cardiovascular (CV) safety by comparing TCZ against current standard of care, TNF inhibitors



50

Case study: Non-randomized database study

ABSTRACT NUMBER: 2611

Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients with Rheumatoid Arthritis

Seoyoung C. Kim[1], Daniel H. Solomon[1], James R. Rogers[1], Sara Gale[2], Micki Klearman[2], Khaled Sarsour[2] and Sebastian Schneeweiss[1], [1]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [2]Genentech, South San Francisco, CA

Meeting: 2016 ACR/ARHP Annual Meeting

Table. HR (95% CI) for composite CV events in TCZ starters versus TNF inhibitors: a 1:3 variable ratio PS-matched analysis

Database	Medicare	IMS	MarketScan	Pooled[3]
As treated	0.76 (0.42, 1.37)	1.11 (0.49, 2.53)	1.01 (0.45, 2.29)	0.90 (0.60, 1.36)
ITT up to 180 days	0.49 (0.21, 1.14)	0.90 (0.32, 2.51)	0.76 (0.26, 2.23)	0.66 (0.38, 1.16)
ITT up to 365 days	0.80 (0.47, 1.38)	0.94 (0.45, 1.95)	0.85 (0.41, 1.76)	0.85 (0.58, 1.23)

51

Case study: ENTRACTE trial

ABSTRACT NUMBER: 3L

Comparative Cardiovascular Safety of Tocilizumab Vs Etanercept in Rheumatoid Arthritis: Results of a Randomized, Parallel-Group, Multicenter, Noninferiority, Phase 4 Clinical Trial

Jon T. Giles[1], Naveed Sattar[2], Sherine E. Gabriel[3], Paul M. Ridker[4], Steffen Gay[5], Charles Warne[6], David Mus... leming[8],

Table. Hazard Ratios of Major End Points for Tocilizumab vs Etanercept

	Etanercept N = 1542	Tocilizumab N = 1538	Tocilizumab vs Etanercept	
	First Events, n	First Events, n	HR[a]	95% CI
MACE-ITT population	**78**	**83**	**1.05**	**0.77, 1.43**
MACE-OT population	52	57	1.11	0.76, 1.62
CVD death	35	36	1.03	0.64, 1.63
Nonfatal MI	31	28	0.89	0.54, 1.49

52

Case study: Comparison

Observational study	ENTRACTE RCT
Multi-database cohort study	Parallel group RCT
TCZ vs. any TNFi	TCZ vs. etanercept
8,790 TCZ patients	1,538 TCZ patients
HR = 0.90 (0.60-1.36) (FDA CV safety: rule out HR of 1.40)	HR = 0.89 (0.54-1.49)
Oct. 2015 – Apr. 2016 (6 months)	Aug 2011 – May 2016 (57 months)
Cost: $y	Cost: 100 X $y
Full transparency via Aetion report	Full transparency via GCP

53

Decision-relevant Evidence

Meaningful

- **Data Quality**
  - Fit for purpose
- **Data Flexibility**
  - Match data type to the question
- **Meaningful statistics**
  - Metrics that matter

Valid

- **Avoid massive design flaws**
  - Think of target trial
- **Approach confounding flexibly**
  - Question & Data type dictate approach
- **Reduce investigator error**
  - Structured approaches

Expedited

- **Speed through closeness to data**
  - Being embedded in the data stream
- **Speed through data standards**
  - Sentinel common data model
- **Speed through analytic tools**
  - Speed without compromising science

Transparent

- **Transparency -> Reproducibility**
  - Be able to reproduce in same data
- **Shared analytics & auditability**
  - Withstand detailed audits of past data
- **Accepted statistical procedure**
  - We have plenty statistical tools

54