Using Healthcare Databases To Evaluate The Safety And Effectiveness Of Newly Marketed Medications

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March 2018

Funding

- This study was funded in part by FDA HHSF223201710186C
- This study was funded in part by the Division of Pharmacoepidemiology
- In addition, Dr. Schneeweiss was funded by PCORI

Disclosures

- PI, Harvard-Brigham & Women's Hospital Drug Safety Research Center (FDA)
- Co-Chair, Methods Core of the FDA Sentinel System
- PI of research grants awarded to BWH by Bayer, Genentech, Boehringer Ingelheim
- Consulting fees from WHISCON, LLC, and Aetion, Inc. (incl. equity)
- Grants/contracts from NIH, AHRQ, PCORI, FDA, IMI, Arnold Foundation

21st Century Cures Act and PDUFA VI: The role of RWE

FDA debates the utility of Real-World Evidence

NEJM 2016;375:2293-7

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.

RWD: Routine data from healthcare systems

JAMA 2017;318:703-4

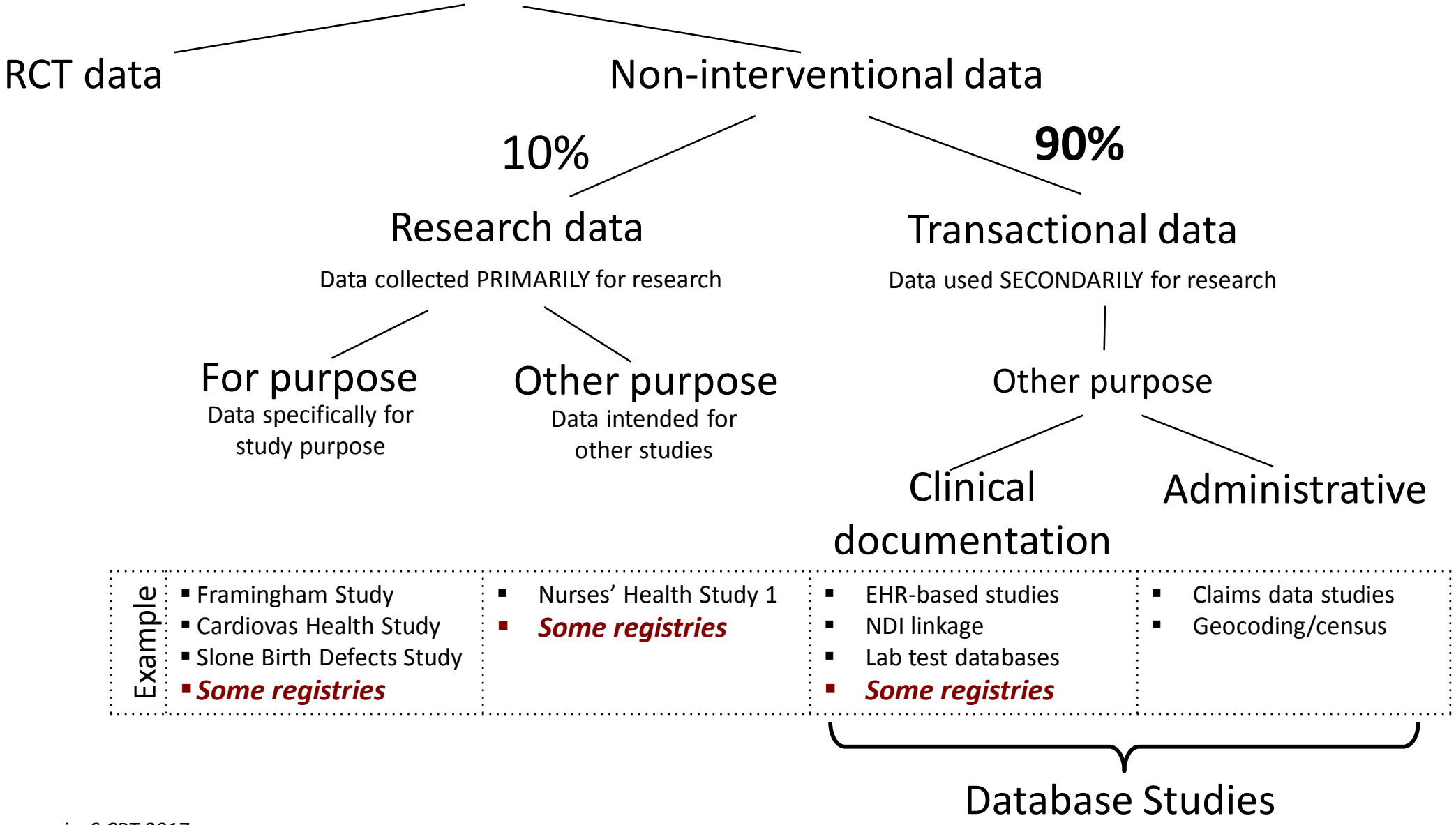
VIEWPOINT

Multidimensional Evidence Generation and FDA Regulatory Decision Making

Defining and Using "Real-World" Data

Jonathan P. Jarow, MD Lisa LaVange, PhD Janet Woodcock, MD

Effectiveness Research with Healthcare Databases



Franklin J, Schneeweiss S CPT 2017

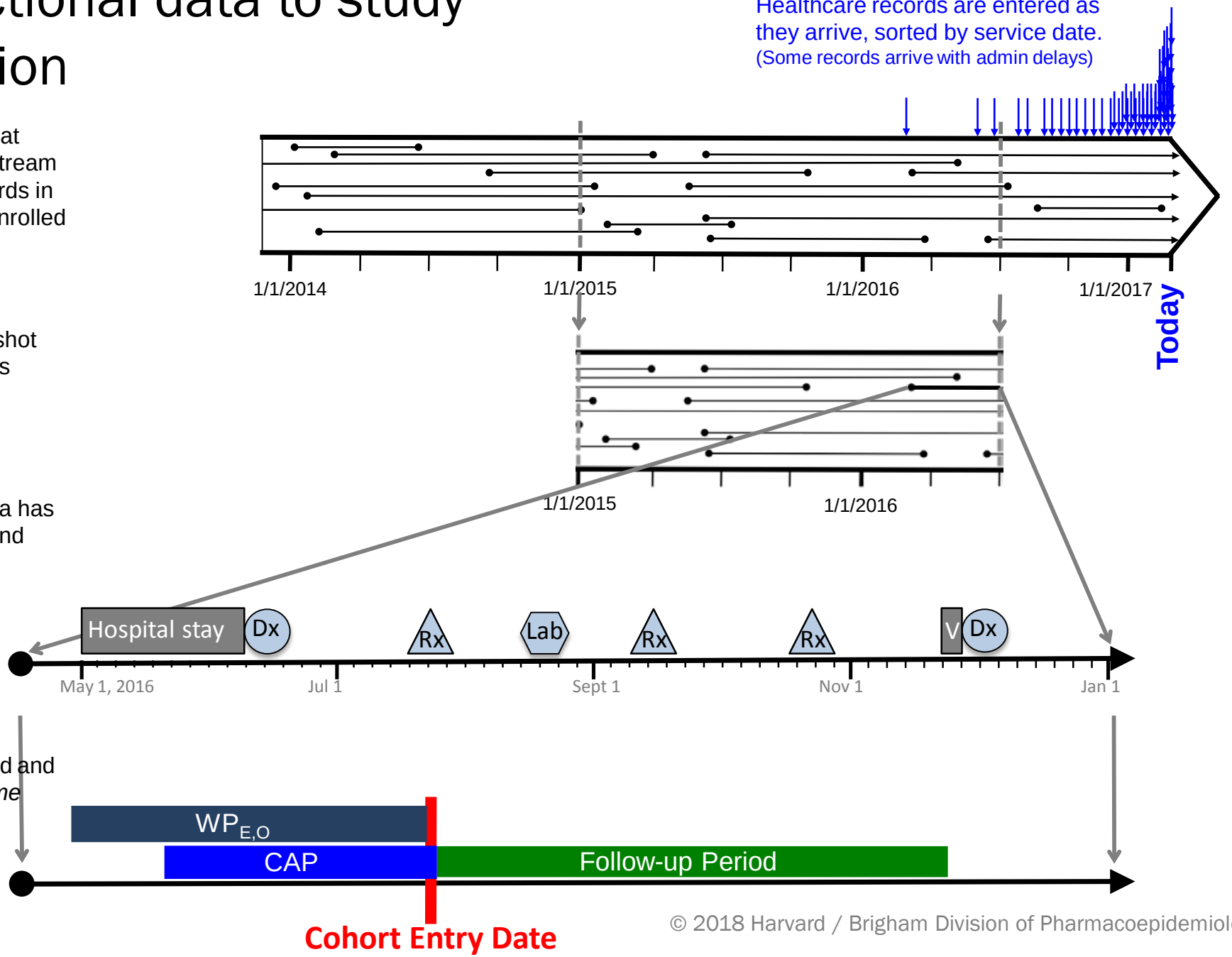
From transactional data to study implementation

Ⓐ Dynamic database that records an ongoing stream of new healthcare records in *Calendar Time* for all enrolled patients: ●——●

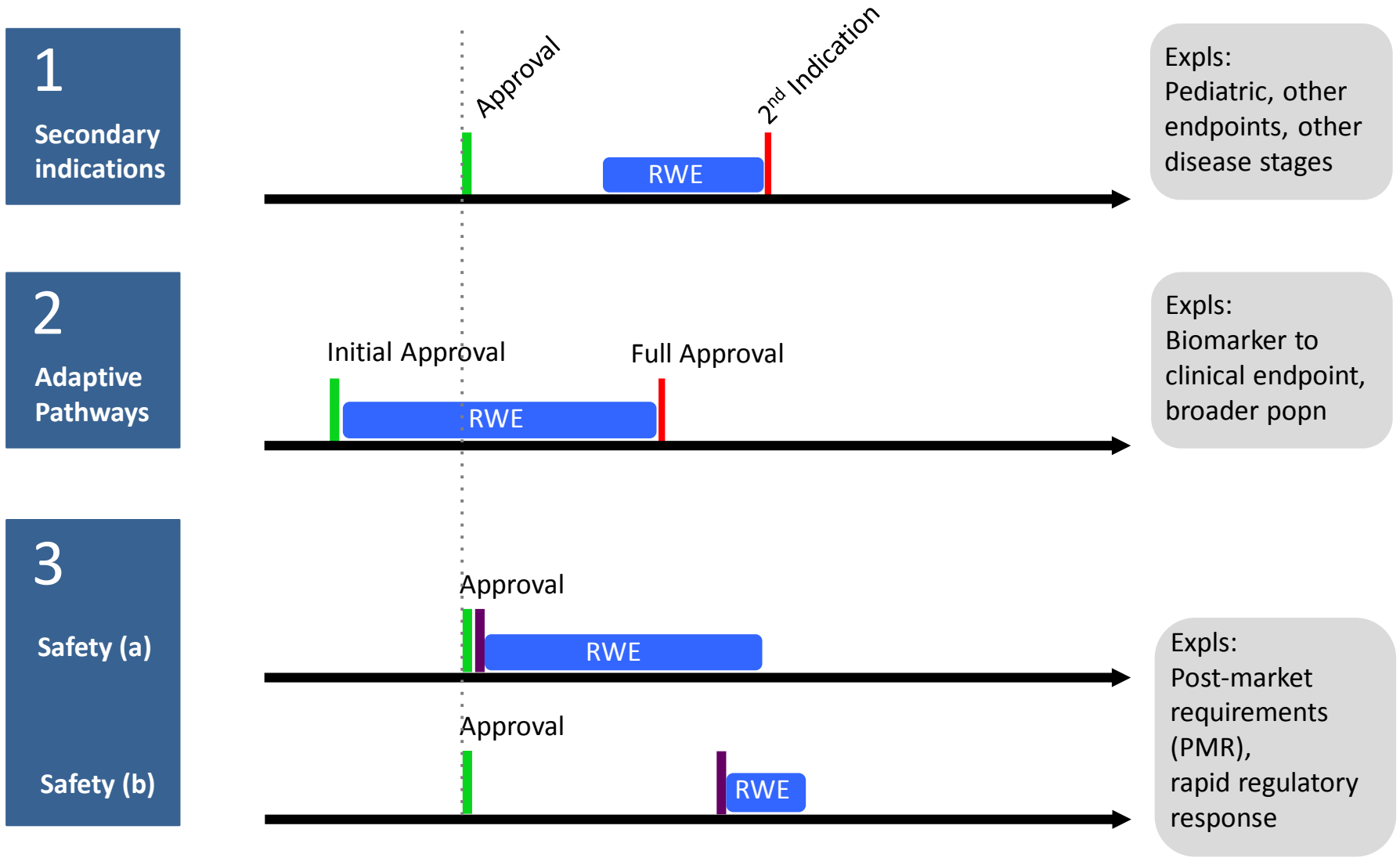
Ⓑ Stabilized data snapshot for research purposes

Ⓒ Individual-patient data has arrived in episodes and from various sources

Ⓓ Study rules are applied and arranged by *Event Time*



RWE in regulatory decision making: Key use cases



Database Study

followed by →

RCT

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 21, 2008 VOL. 358 NO. 8

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.

Risk of death (7d)

HR = 1.78 (1.56 -2.02)

Outcome	Any Amount of Aprotinin (N=33,517)	Any Amount of Aminocaproic Acid (N=44,682)	Any Amount of Study Drug		Low or High Amount of Study Drug
			Unadjusted	Adjusted	Adjusted
	no. of patients (%)		*relative risk (95% CI)*		
In-hospital death from any cause	1512 (4.5)	1101 (2.5)	1.83 (1.70–1.98)	1.64 (1.50–1.78)	1.50 (1.36–1.66)
In-hospital death from any cause within 7 days after CABG	631 (1.9)	435 (1.0)	1.93 (1.71–2.18)	1.78 (1.56–2.02)	1.64 (1.41–1.91)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 29, 2008 VOL. 358 NO. 22

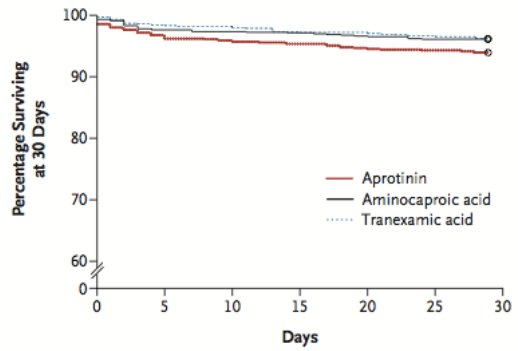
A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery

Dean A. Fergusson, M.H.A., Ph.D., Paul C. Hébert, M.D., M.H.Sc., G. David Mazer, M.D., Stephen Fremes, M.D., Charles MacAdams, , Peter C. Duke, M.D., Ramiro Arellano, M.D., M.Sc., Côté, M.D., Jacek Karski, M.D., Raymond Martineau, M.D., , M.Sc., George Wells, Ph.D., Jennifer Clin nvestigators†

BART

Risk of death (30d)

HR = 1.53 (1.06 -2.22)



No. at Risk							
Aprotinin	779	753	747	742	737	734	732
Aminocaproic acid	780	761	759	757	753	749	749
Tranexamic acid	769	757	755	748	747	743	749

Database Study

followed by →

RCT

ARTHRITIS & RHEUMATOLOGY

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

A Multi-Database Cohort Study

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]

Risk of composite CV outcome

HR = 0.85 (0.61-1.19)

	TCZ				
	No. of subjects	No. of events	Person-years	IR (95% CI)†	HR (95% CI)
As-treated analysis					
Composite cardiovascular events					
Medicare	2,531	17	1,841	0.92 (0.56–1.44)	0.70 (0.40–1.24)
PharMetrics	2,614	10	2,061	0.49 (0.25–0.86)	1.00 (0.45–2.22)
MarketScan	4,073	9	2,999	0.30 (0.15–0.55)	1.03 (0.46–2.34)
Combined	9,218	36	6,901	0.52 (0.37–0.71)	0.84 (0.56–1.26)‡

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

ENTRACTE

Jon T. Giles[1], Naveed Sattar[2], Sherine E. Gabriel[3], Paul M. Ridker[4], Steffen Gay[5], Charles Warne[6], David Musselman[7], Laura Brockwell[6], Emma Shittu[6], Micki Klearman[7] and Thomas Fleming[8],

Risk of composite CV outcome

HR = 1.05 (0.77-1.43)

Etanercept N = 1542	Tocilizumab N = 1538	Tocilizumab vs Etanercept	
First Events, n	First Events, n	HR[a]	95% CI
78	83	1.05	0.77, 1.43

RCT *followed by* → Database Study

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Ma…s, Dr.P.H., Odd Erik Johansen, …i C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

EMPA-REG

Empagliflozin and risk of DKA

1 / 2,333 vs. 3 / 2,345

HR = 2.9 (0.4-20.0)

Table 2. Adverse Events.*

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
		number of patients (percent)		
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)

CORRESPONDENCE

Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor

Michael Fralick, M.D.
Sebastian Schneeweiss, M.D., Sc.D.
Elisabetta Patorno, M.D., Dr.P.H.

SGLT-2 and risk of DKA

26 / 38,045 vs. 55 / 38,045

HR = 2.2 (1.4-3.6)

Table 2. Primary and Other Outcomes.*

Days of Follow-up	DPP4 Inhibitor (N=38,045)		SGLT2 Inhibitor (N=38,045)	
	Diabetic Ketoacidosis	Hazard Ratio	Diabetic Ketoacidosis	Hazard Ratio (95% CI)
	no. of patients (rate per 1000 person-yr)		*no. of patients (rate per 1000 person-yr)*	
180 Days of follow-up†	26 (2.2)	1.0	55 (4.9)	2.2 (1.4–3.6)
60 Days of follow-up	13 (2.3)	1.0	31 (5.6)	2.5 (1.3–4.7)
30 Days of follow-up	10 (3.3)	1.0	22 (7.5)	2.3 (1.1–4.8)
180 Days of follow-up among patients not receiving insulin‡	9 (1.0)	1.0	21 (2.5)	2.5 (1.1–5.5)

RCT *followed by* → Database Study

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

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.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeann... D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M... oph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., ...tee and Investigators*

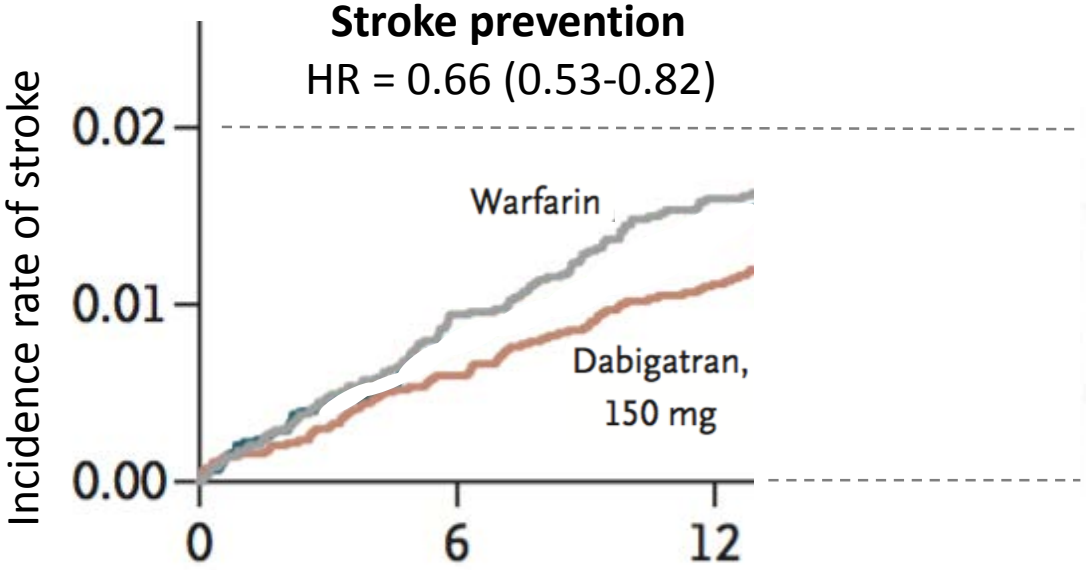
RE-LY

Thrombosis and Haemostasis
International Journal for Vascular Biology and Medicine

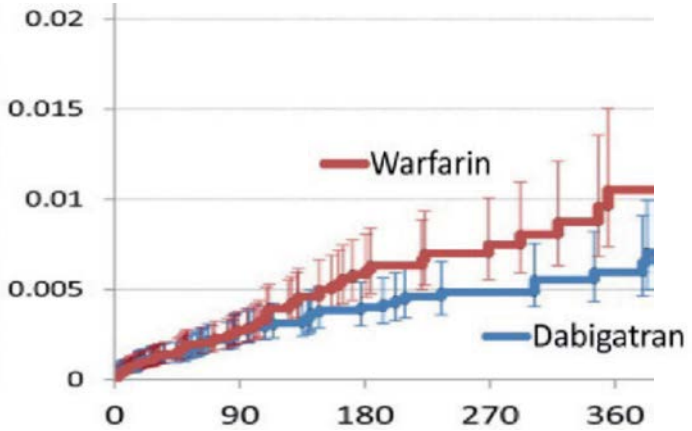
Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation

John D. Seeger[1]; Katsiaryna Bykov[1]; Dorothee B. Bartels[2,3]; Krista Huybrechts[1]; Kristina Zint[2]; Sebastian Schneeweiss[1]

Stroke prevention
HR = 0.66 (0.53-0.82)



Stroke prevention
HR = 0.77 (0.54-1.09)



Database Study

followed by →

RCT

Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study

Elisabetta Patorno,[1] Allison B Goldfine,[2] Sebastian Schneeweiss,[1] Bre
Robert J Glynn,[1] Jun Liu,[1] Seoyoung C Kim[1,4]

BMJ

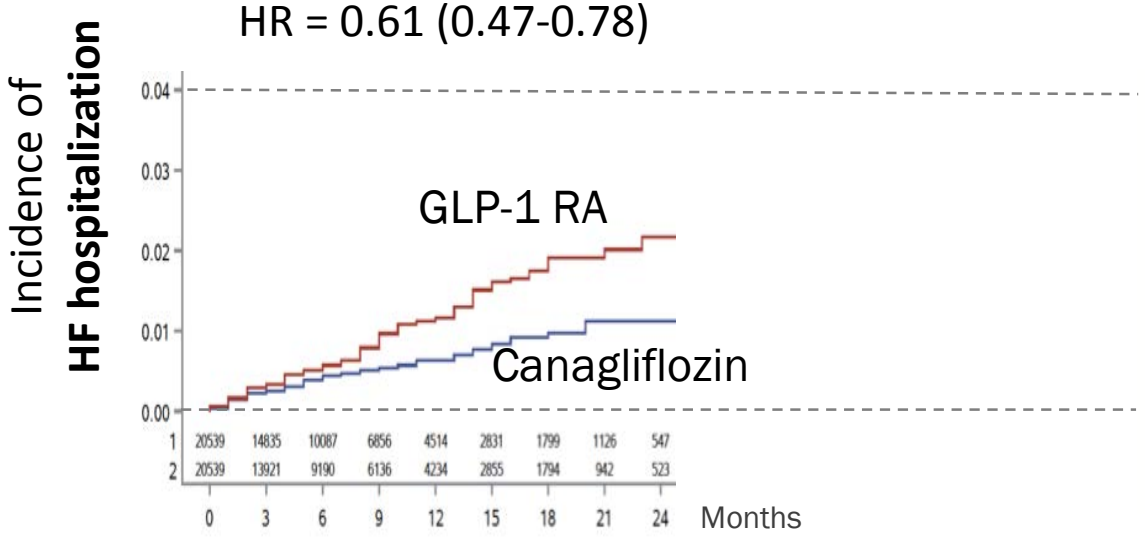
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D.,
Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D.,
Ngozi Erondu, M... Law, Ph.D.,
Mehul Desai, M... M., B.Ch.,
for the...

CANVAS

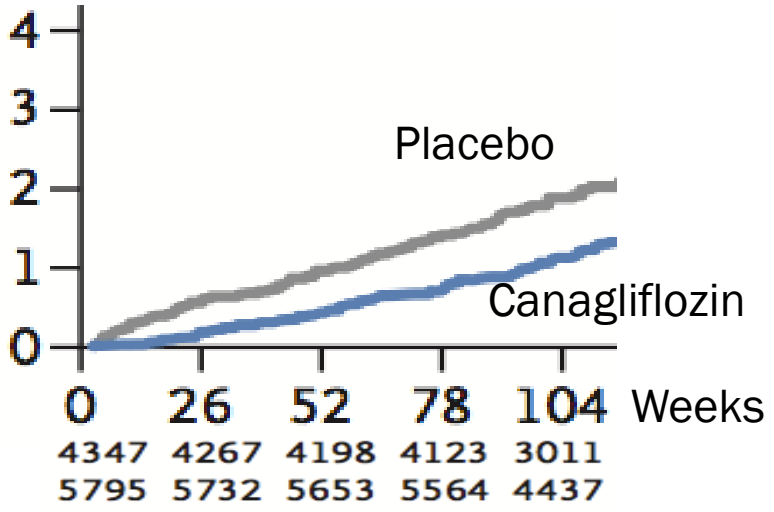
Prevention of heart failure hospitalization

HR = 0.61 (0.47-0.78)



Prevention of heart failure hospitalization

HR = 0.67 (0.52-0.87)



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

American Diabetes Association. 77TH SCIENTIFIC SESSIONS
EXPERIENCE NEW HORIZONS IN DIABETES
SAN DIEGO, CA JUNE 9-13, 2017

Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study

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BMJ

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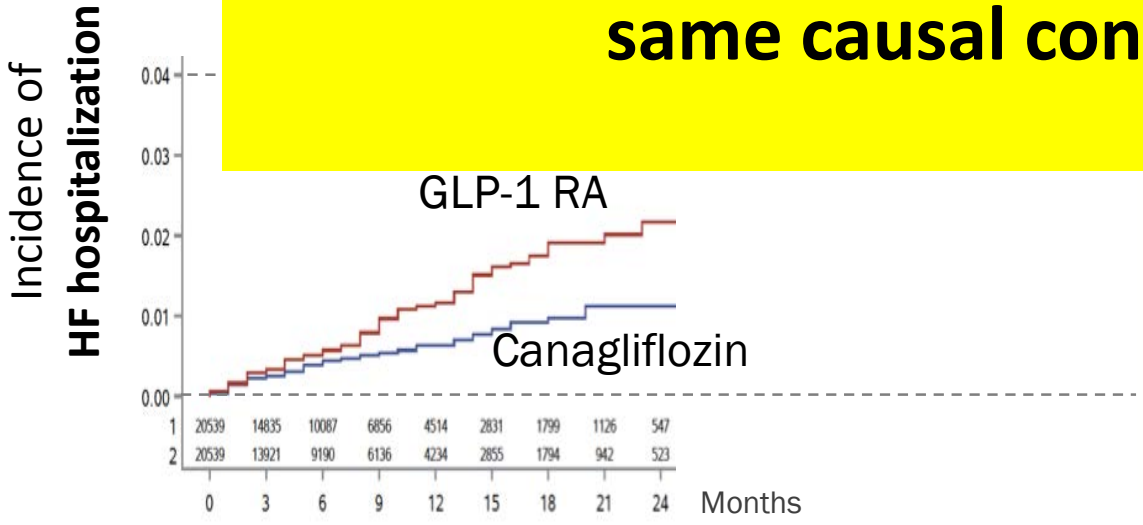
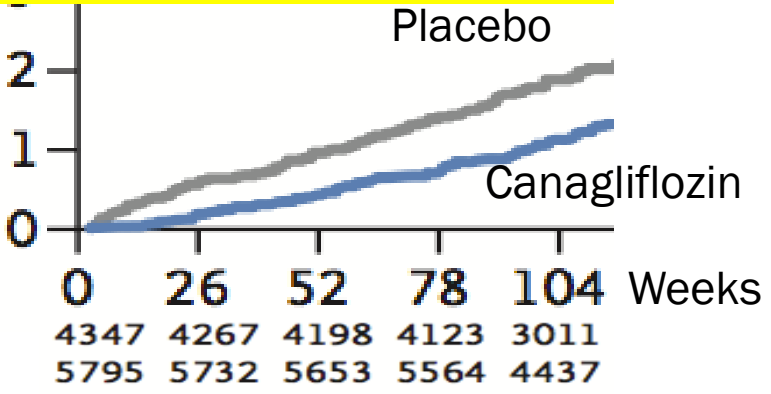
Mehul Desai, M... M., B.Ch.,

CANVAS

Why did these database studies come to the same causal conclusion?





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

Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study

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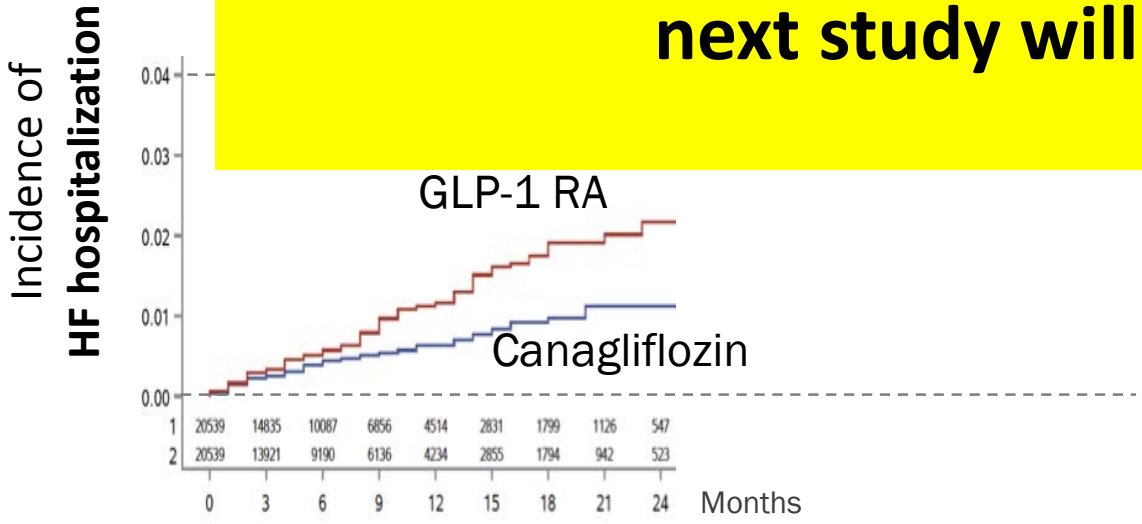
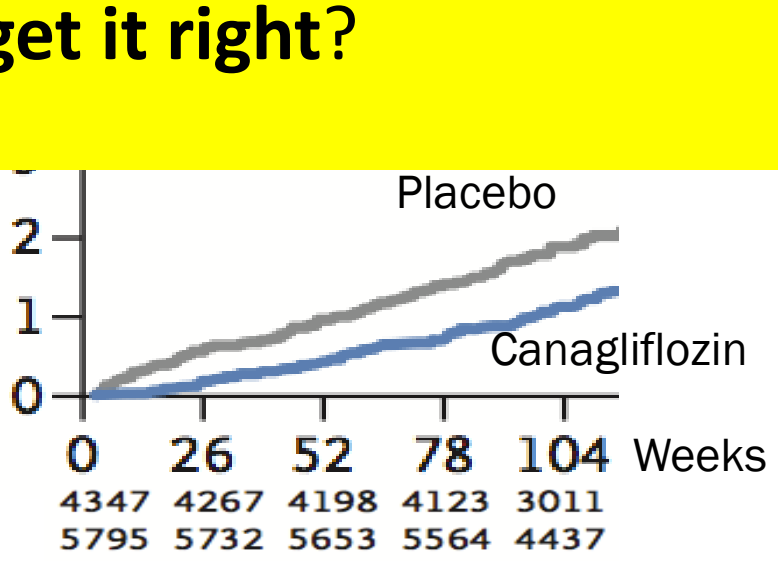
CANVAS

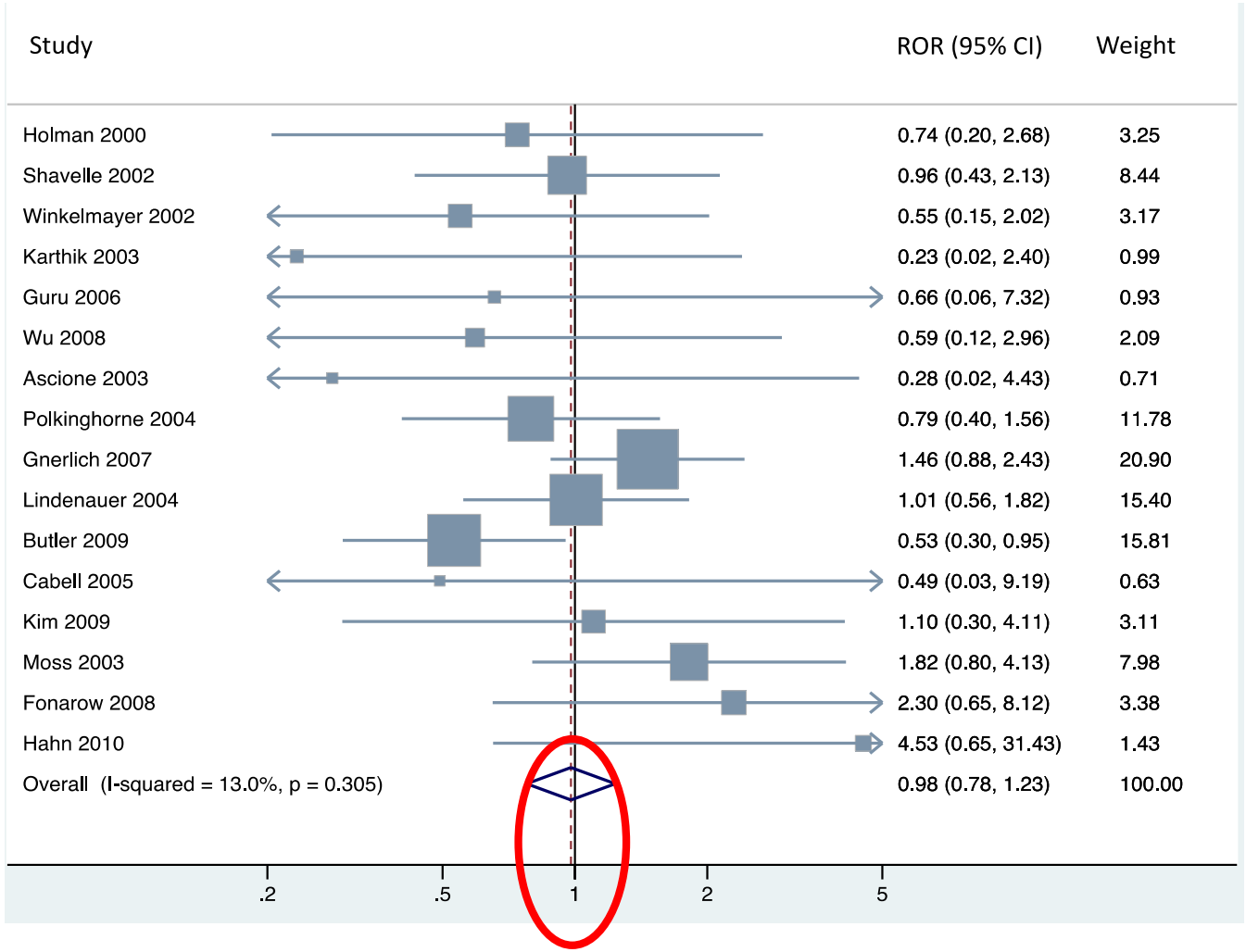
How confident are we that the **next study will get it right**?





Re-analysis of Hemkens et al. BMJ 2016

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



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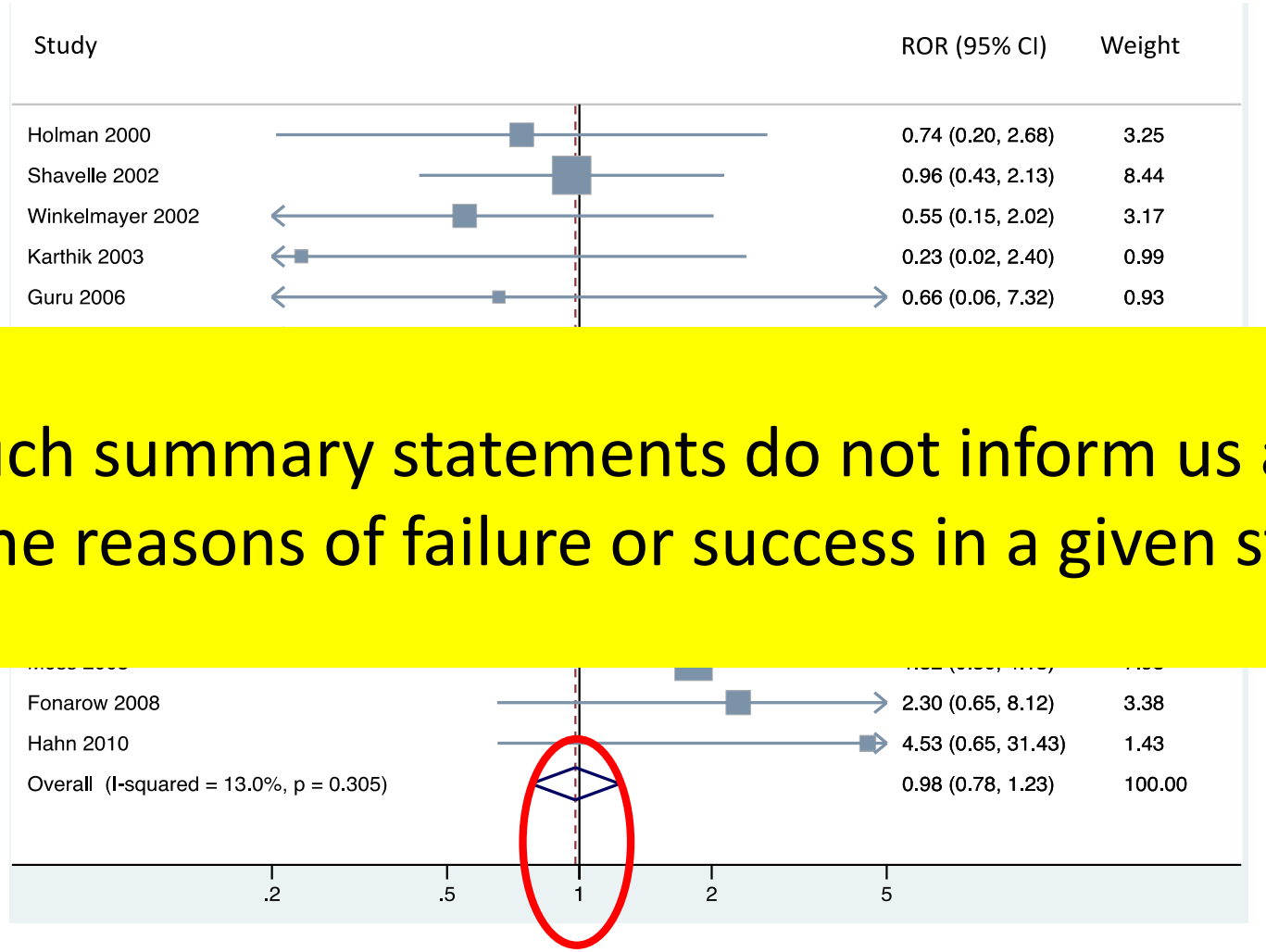
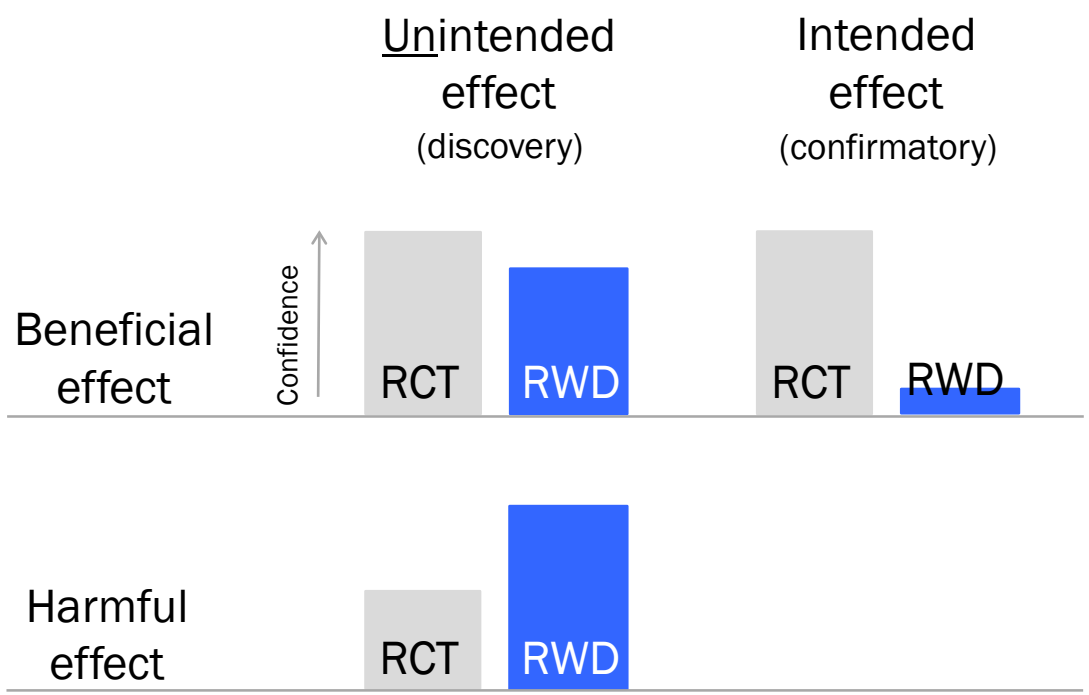


Such summary statements do not inform us about the reasons of failure or success in a given study.

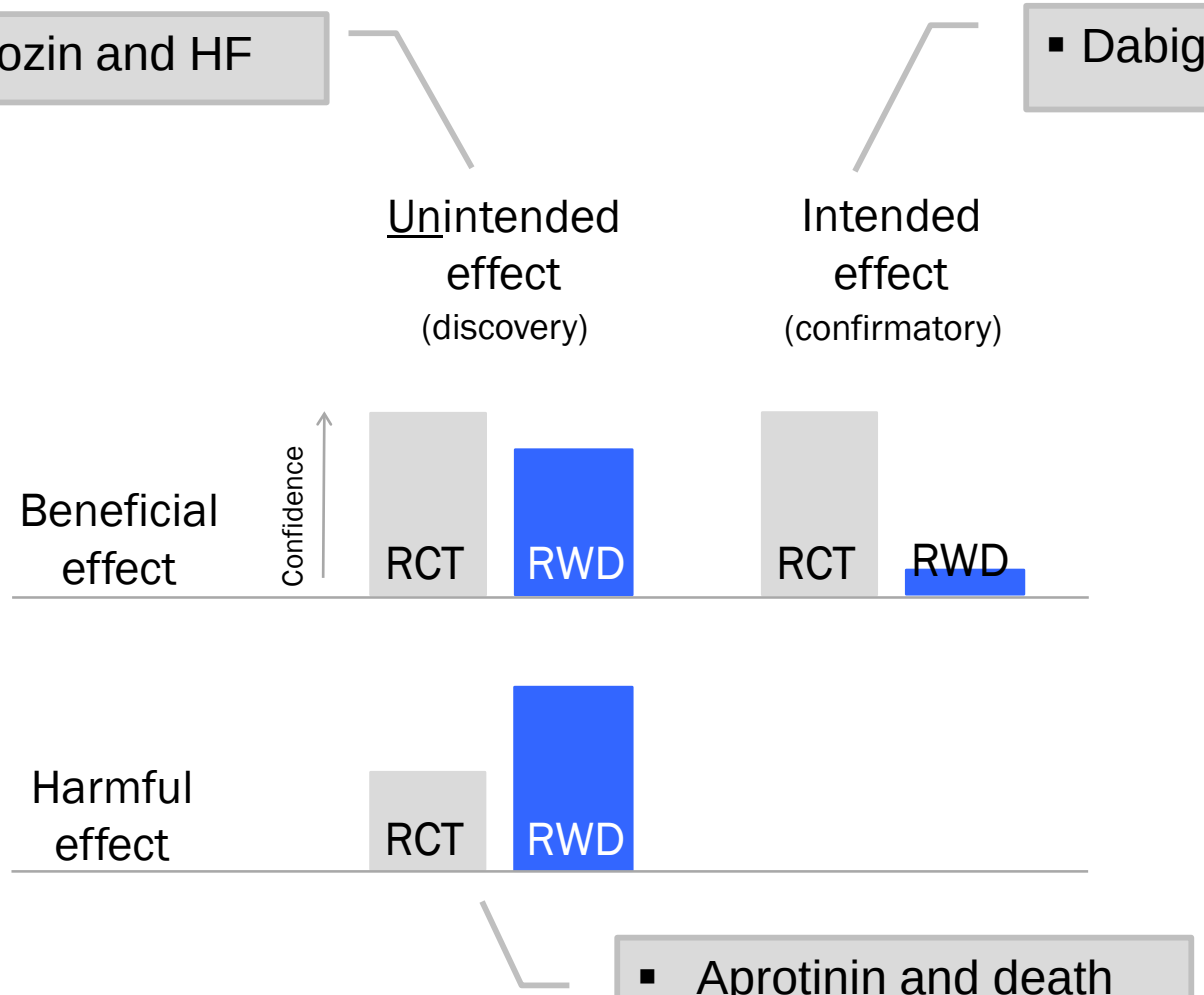
Confidence in validity of study findings



Confidence in validity of study findings

- Canagliflozin and HF

- Dabigatran and stroke



- Aprotinin and death
- Tociluzimab and CVD
- SGLT-2 and DKA

A spectrum of choices for decision makers

Strongly prefer RCT

RWD analysis possible

This talk

Reminder: Why we love RCTs

Randomized Controlled Trials

Random treatment assignment

Controlled outcome measurement

Clear and easy to understand implementation

When to do database studies?

Study question -dependent

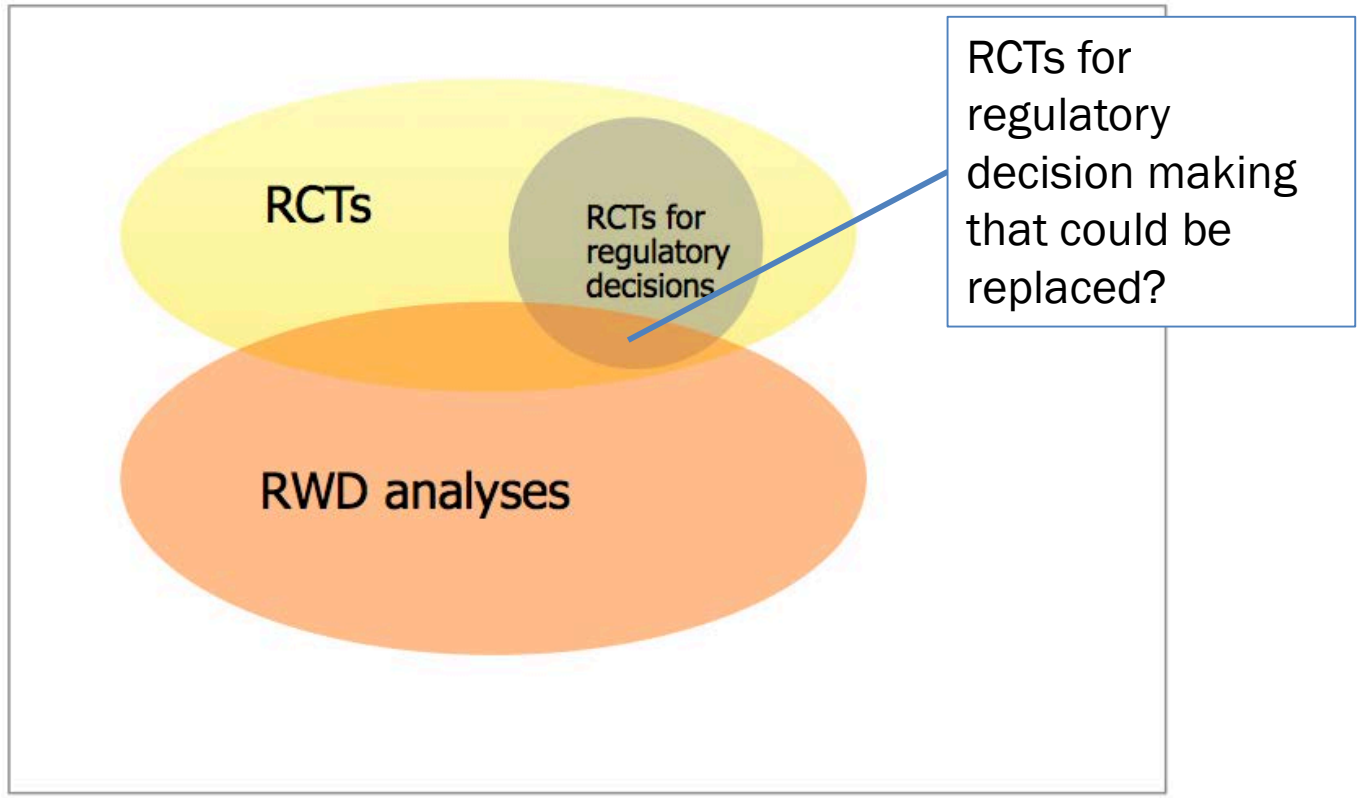
1. Active comparator preferred
2. Outcome, exposure measurable
3. Key confounders measurable

When to do database studies?

Study question -dependent

1. Active comparator preferred
2. Outcome, exposure measurable
3. Key confounders measurable

The universe of study questions validly answerable



How to …

Data-dependent

4. Proceed if
   a) Outcome observable with specificity
   b) Sufficient outcome surveillance
   c) Sufficient patient similarity is reached[1)]

Investigator-controlled

5. Avoid known design and analytic flaws:
   a) Avoid immortal time bias
   b) Avoid adjusting for causal intermediates
   c) Avoid reverse causation
   d) Deal with time-varying hazards

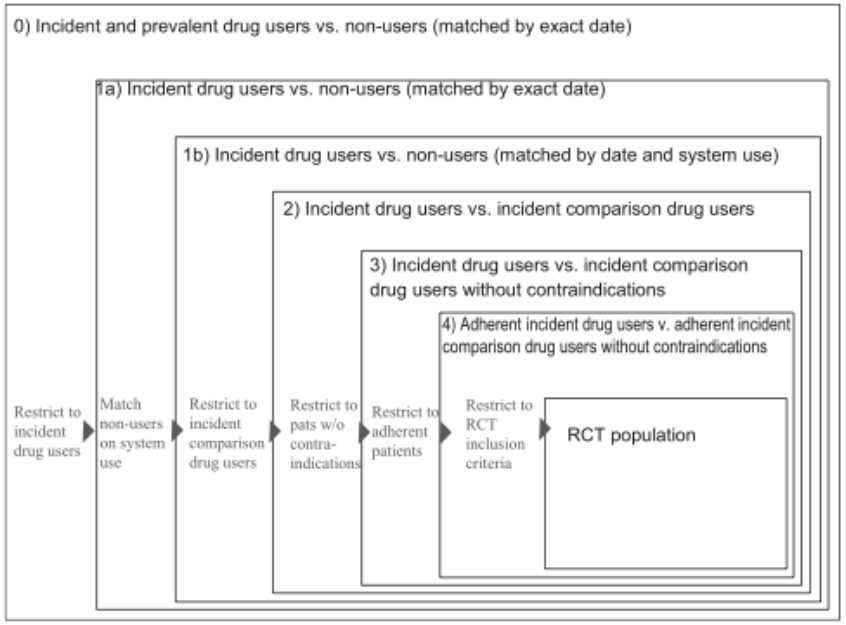
6. Do robustness checks
   a) Negative/positive controls
   b) Check balance of unmeasured factors

1) *Franklin et al. Epidemiology 2014*

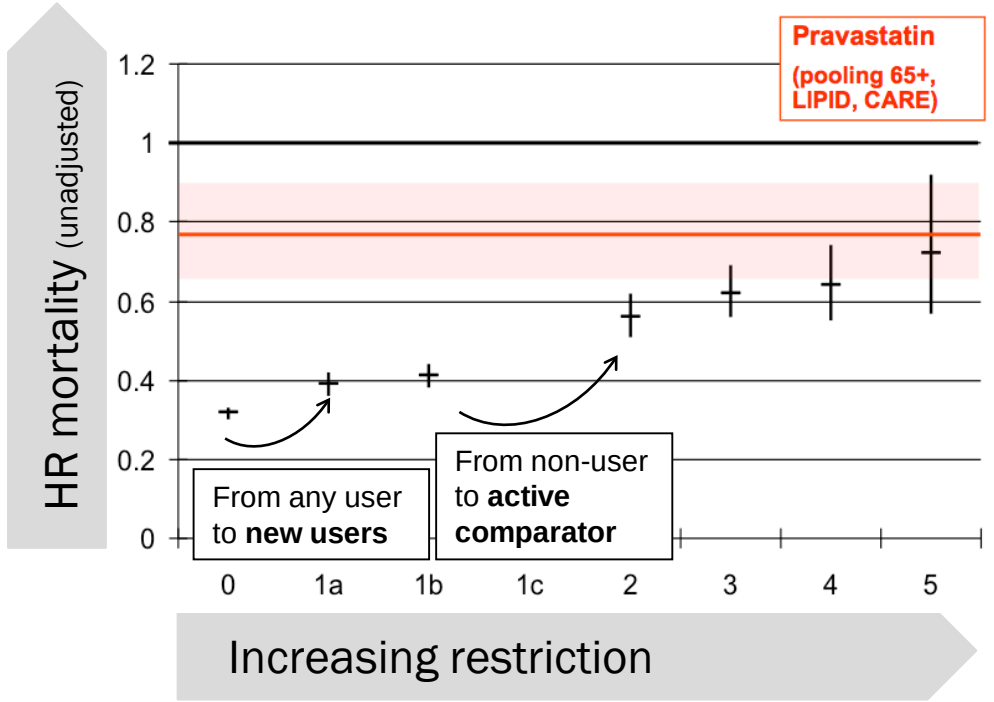
The advantages of an **active comparator new user design** has been demonstrated many times: Example Statin and mortality

Increasing Levels of Restriction in Pharmacoepidemiologic Database Studies of Elderly and Comparison With Randomized Trial Results

Sebastian Schneeweiss, MD, ScD, Amanda R. Patrick, MS,* Til Stürmer, MD, MPH,* M. Alan Brookhart, PhD,* Jerry Avorn, MD,* Malcolm Maclure, ScD,* Kenneth J. Rothman, DMD, DrPH,† and Robert J. Glynn, PhD, ScD**



Increasing restriction of a broad RWD population leads to a narrow RCT population



The observed effect size is moving to the RCT finding with increasing restriction even w/o statistical adjustment

Schneeweiss et al Med Care 2007

How to …

Data-dependent

4. Proceed if
   a) Outcome observable with specificity
   b) Sufficient outcome surveillance
   c) Sufficient patient similarity is reached[1)]

Investigator-controlled

5. Avoid known design and analytic flaws:
   a) Avoid immortal time bias
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   c) Avoid reverse causation
   d) Deal with time-varying hazards

6. Do robustness checks
   a) Negative/positive controls
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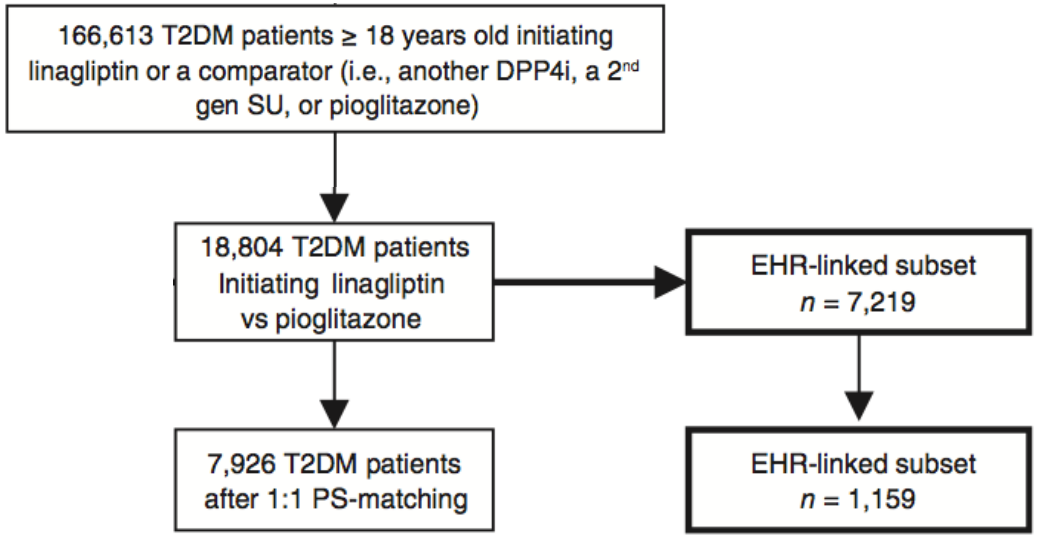
1) *Franklin et al. Epidemiology 2014*

Checking balance of unmeasured covariates in EHR-defined measures

Claims-defined
120 variables in 1:1 PS matching

Claims-based patient characteristics
Demographics
Mean (SD) age
Female, %
Features of medication initiation, %
Monotherapy
Dual therapy
Therapy with >2 agents
Dual therapy with metformin[a]
Concomitant initiation of other antidiabetic agents, %
Concomitant initiation of metformin
Concomitant initiation of insulin
Current use of other antidiabetic agents[b], %
Current use of metformin
Current use of insulin
Comorbidities at baseline, %
Mean (SD) Charlson comorbidity score
Diabetic nephropathy, %
Diabetic retinopathy, %
Diabetic neuropathy, %
Peripheral vascular disease, %
Erectile dysfunction, %
Diabetic foot, %
Skin infections, %
Hypoglycaemia, %
Hypertension, %
Hyperlipidaemia, %
Coronary atherosclerosis, %
Acute myocardial infarction, %
Old myocardial infarction, %
Unstable angina, %
Stable angina, %
Other chronic ischaemic heart disease, %
Coronary procedure (CABG or PTCA), %
History of PTCA or CABG, %
Ischaemic stroke, %
Congestive heart failure, %
Renal dysfunction, %
Oedema, %

Linagliptin vs. pioglitazone and CV endpoints



EHR-defined
6 variables for balance checking

- Smoking
- BMI
- DM duration
- Hb_{A1C}
- eGFR
- LDL

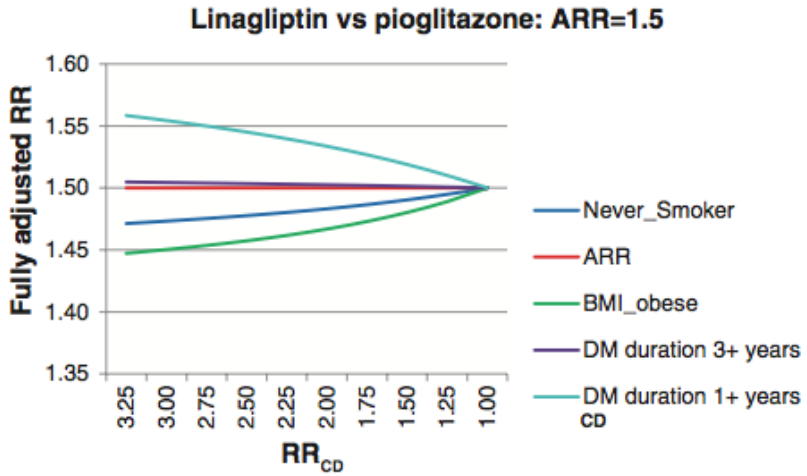
Patorno et al. Diabetes Obes Metab 2018

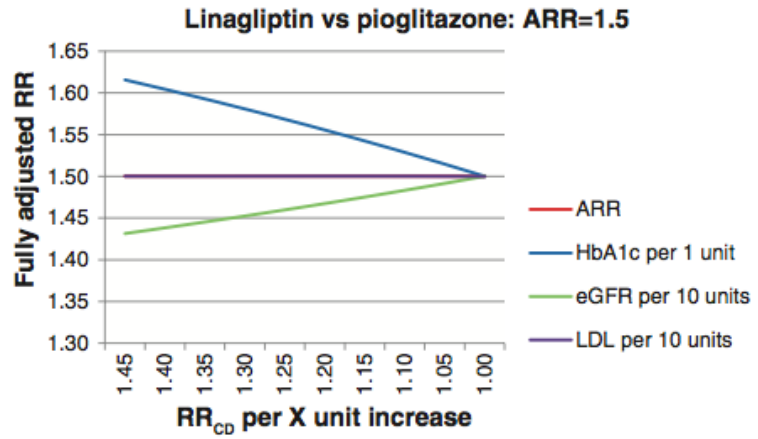
Checking balance of unmeasured covariates in EHR-defined measures

Balance Analysis

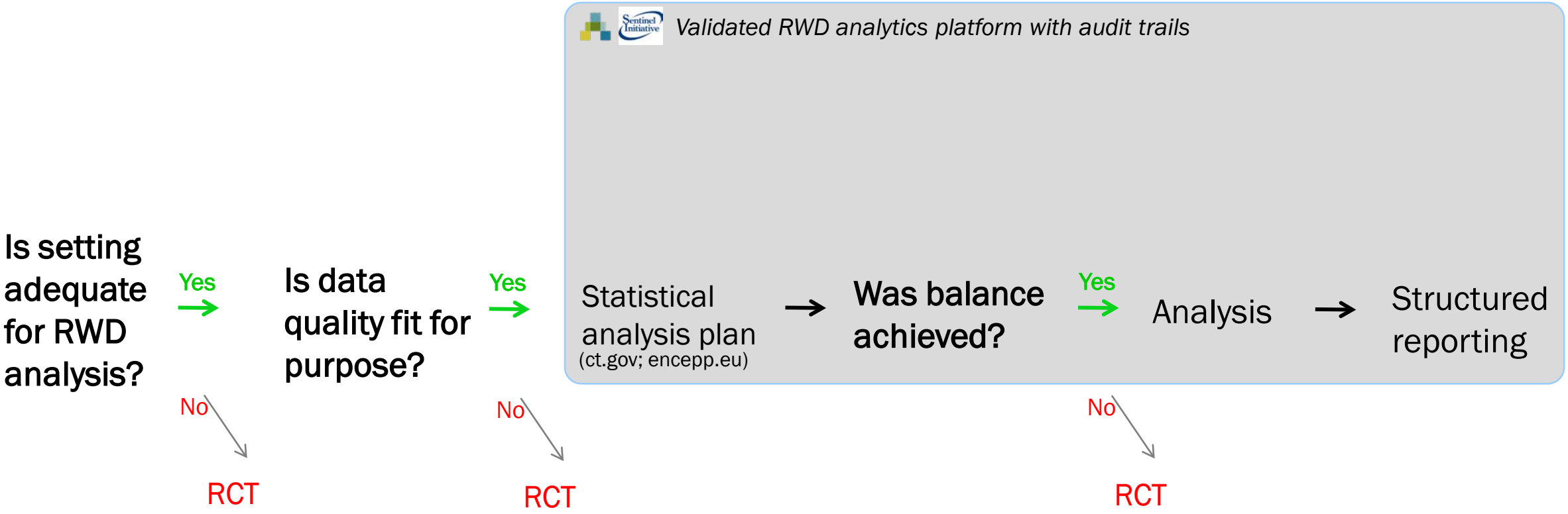
	Linagliptin	Pioglitazone
Never smoking	32.4%	33.9%
Obese	49.4%	46.1%
>3 years DM duration	17.7%	20.1%
Hb_{A1C}, %	8.0 (7.1-9.1)	8.2 (7.1-9.9)
eGFR, ml/min/1.73m^2	102 (93-116)	104 (96-118)
LDL, mg/dl	97 (73-116)	97 (79-115)

Sensitivity Analysis

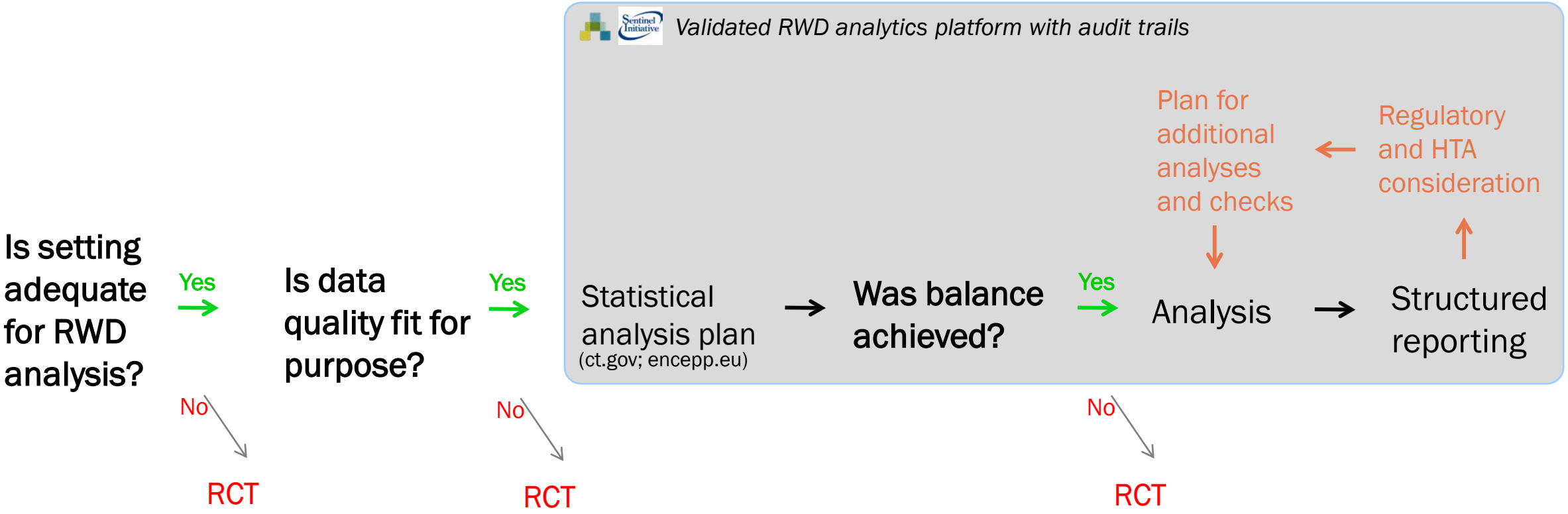




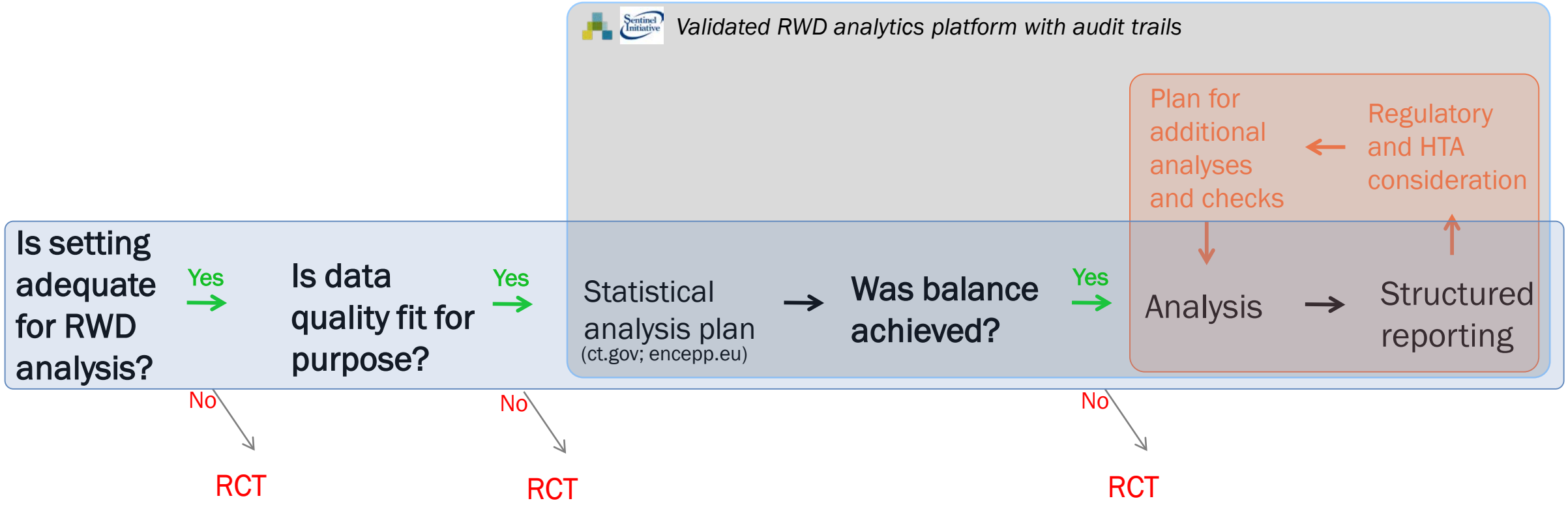
A pathway



A pathway with regulatory validation



A pathway with regulatory validation



Case study: Telmisartan

Telmisartan is an angiotensin receptor blocker (ARB)

Original indication in 1998:

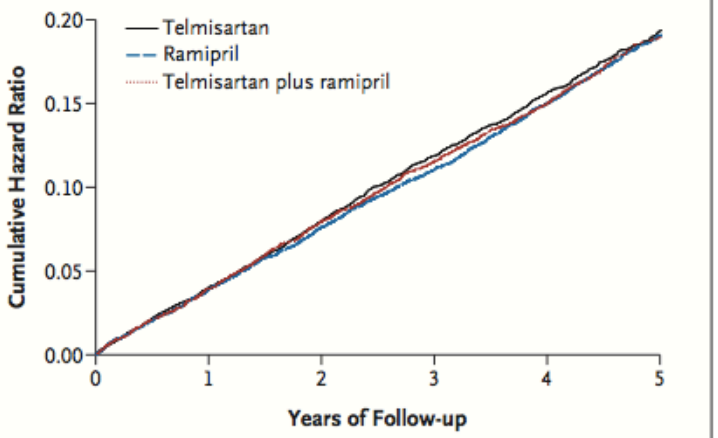
- Hypertension

Supplementary indication in 2009:

- Cardiovascular risk reduction in patients ≥55 years

ONTARGET trial:

- Telmisartan (ARB) vs. Ramipril (ACE)
- CV death, MI, stroke, heart failure hospitalization



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

Case study: Telmisartan

- Let us say we have healthcare claims data available to us
- Let us say we have claims from commercial US insurer, e.g. MarketScan, from 2003 through 2009 (130 million lives covered).

JAMA Internal Medicine | Original Investigation

Use of Health Care Databases to Support Supplemental Indications of Approved Medications

Michael Fralick, MD; Aaron S. Kesselheim, MD, JD, MPH; Jerry Avorn, MD; Sebastian Schneeweiss, MD, ScD

Invited Commentary

Comparison of Observational Data and the ONTARGET Results for Telmisartan Treatment of Hypertension

Bull's-eye or Painting the Target Around the Arrow?

Robert M. Califf, MD

Case study: Telmisartan

New user, active comparator, PS-matched cohort study

Table 1. Baseline characteristics prior to receiving telmisartan or ramipril

	Unmatched Population			PS-Matched Population		
	Ramipril (N=48,053)	Telmisartan (N=4665)	SD	Ramipril (N=4665)	Telmisartan (N=4665)	SD
Mean age (S. Dev.)	68.29 (9.52)	69.43 (9.60)	0.119	69.36 (9.67)	69.43 (9.60)	0.007
Age category			0.149			0.031
55-60	9,747 (20.3%)	802 (17.2%)		839 (18.0%)	802 (17.2%)	
60-65	11,539 (24.0%)	985 (21.1%)		947 (20.3%)	985 (21.1%)	
65-70	6,262 (13.0%)	626 (13.4%)		655 (14.0%)	620 (13.4%)	
70-75	6,468 (13.5%)	681 (14.6%)		666 (14.3%)	681 (14.6%)	
≥75	14,037 (29.2%)	1,571 (33.7%)		1,558 (33.4%)	1,571 (33.7%)	
Male	31,940 (66.5%)	2,413 (51.7%)	0.303	2,343 (50.2%)	2,413 (51.7%)	0.03
Date of cohort entry			0.046			0.053
First Quarter	13,667 (28.4%)	1,198 (25.7%)		1,149 (24.6%)	1,198 (25.7%)	
Second Quarter	10,080 (21.0%)	1,038 (22.3%)		1,005 (21.5%)	1,038 (22.3%)	
Third Quarter	12,730 (26.5%)	1,310 (28.1%)		1,395 (29.9%)	1,310 (28.1%)	
Fourth Quarter	11,576 (24.1%)	1,119 (24.0%)		1,116 (23.9%)	1,119 (24.0%	

Case study: Telmisartan

Balanced patient characteristics after PS-matching

Comorbid Conditions						
Hypertension	21,361 (44.5%)	2,835 (60.8%)	0.331	2,832 (60.7%)	2,835 (60.8%)	0.001
Coronary artery disease	37,591 (78.2%)	3,105 (66.6%)	0.263	3,053 (65.4%)	3,105 (66.6%)	0.024
Diabetes Mellitus	14,375 (29.9%)	1,524 (32.7%)	0.059	1,514 (32.5%)	1,524 (32.7%)	0.005
PAD	2,651 (5.5%)	362 (7.8%)	0.09	355 (7.6%)	362 (7.8%)	0.006
Stroke or TIA	5,727 (11.9%)	730 (15.6%)	0.108	783 (16.8%)	730 (15.6%)	0.031
Angina	11,272 (23.5%)	815 (17.5%)	0.149	817 (17.5%)	815 (17.5%)	0.001
Heart failure	7,205 (15.0%)	510 (10.9%)	0.121	526 (11.3%)	510 (10.9%)	0.011
Renal disease	3,549 (7.4%)	545 (11.7%)	0.147	515 (11.0%)	545 (11.7%)	0.02
Smoking	1,734 (3.6%)	115 (2.5%)	0.067	128 (2.7%)	115 (2.5%)	0.017
Previous CABG or PCI	5,454 (11.3%)	124 (2.7%)	0.346	111 (2.4%)	124 (2.7%)	0.018
Medications						
Statin	22,441 (46.7%)	2,104 (45.1%)	0.032	2,073 (44.4%)	2,104 (45.1%)	0.013
Beta-Blocker	20,957 (43.6%)	1,926 (41.3%)	0.047	1,913 (41.0%)	1,926 (41.3%)	0.006
Anti-platelet agent	11,031 (23.0%)	1,127 (24.2%)	0.028	1,148 (24.6%)	1,127 (24.2%)	0.01
Calcium-channel blocker	5,386 (11.2%)	833 (17.9%)	0.189	825 (17.7%)	833 (17.9%)	0.004
Diuretic	11,396 (23.7%)	1,342 (28.8%)	0.115	1,325 (28.4%)	1,342 (28.8%)	0.008
ACE or ARB use	0 (0%)	0 (0%)	0	0 (0%)	0 (0%)	0

Case study: Telmisartan

Comparing RWE vs. RCT results

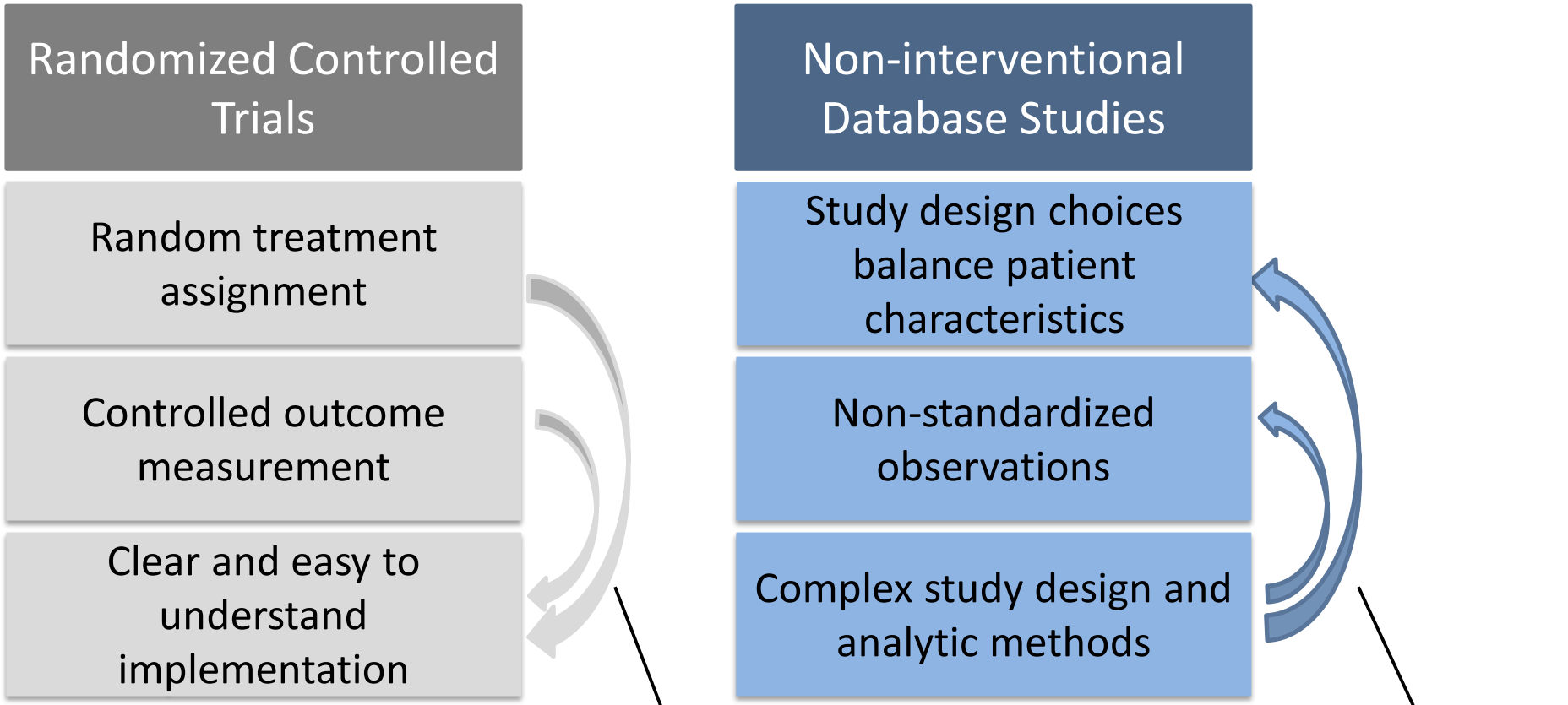
	Observational Cohort Study		ONTARGET Clinical Trial	
	Ramipril (N=4,665)	Telmisartan (N=4,665)	Ramipril (N = 8576)	Telmisartan (N = 8542)
Composite endpoint	Ref.	0.99 (0.85, 1.14)*	1.01 (0.94, 1.09)	
Stroke	Ref.	0.95 (0.71, 1.26)*	0.91 (0.70, 1.05)	
Myocardial infarction	Ref.	0.92 (0.67, 1.27)*	1.07 (0.94, 1.22)	
Hospitalization for heart failure	Ref.	0.95 (0.79, 1.13)*	1.12 (0.97, 1.29)	
Angioedema	Ref.	0.13 (0.03, 0.56)*	0.4 (p=0.01)**	

Case study: Telmisartan

Comparing RWE vs. RCT results

	Observational Cohort Study		ONTARGET Clinical Trial	
	Ramipril (N=4,665)	Telmisartan (N=4,665)	Ramipril (N = 8576)	Telmisartan (N = 8542)
Composite endpoint	Ref.	0.99 (0.85, 1.14)*	1.01 (0.94, 1.09)	
Stroke	Ref.	0.95 (0.71, 1.26)*	0.91 (0.70, 1.05)	
Myocardial infarction	Ref.	0.92 (0.67, 1.27)*	1.07 (0.94, 1.22)	
Hospitalization for heart failure	Ref.	0.95 (0.79, 1.13)*	1.12 (0.97, 1.29)	
Angioedema	Ref.	0.13 (0.03, 0.56)*	0.4 (p=0.01)**	

Transparency to increase confidence in RWD analyses



Controlled study environment and self-evident methodology provides confidence in decision making

Transparent, structured reporting of complex methodology clarifies study validity for decision makers

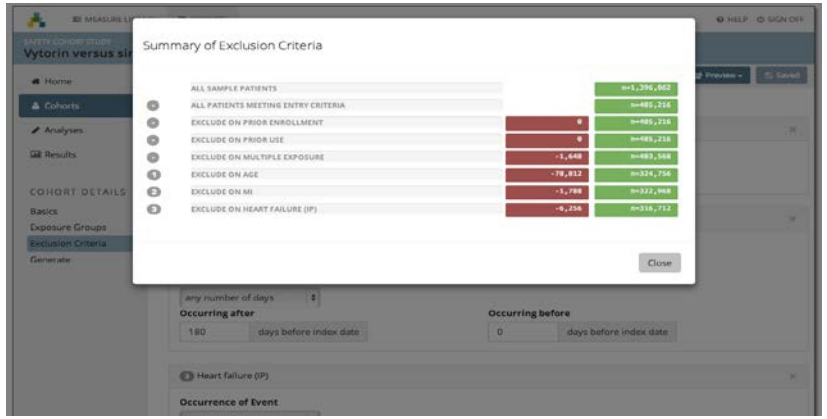
How to …

Quality Improvement

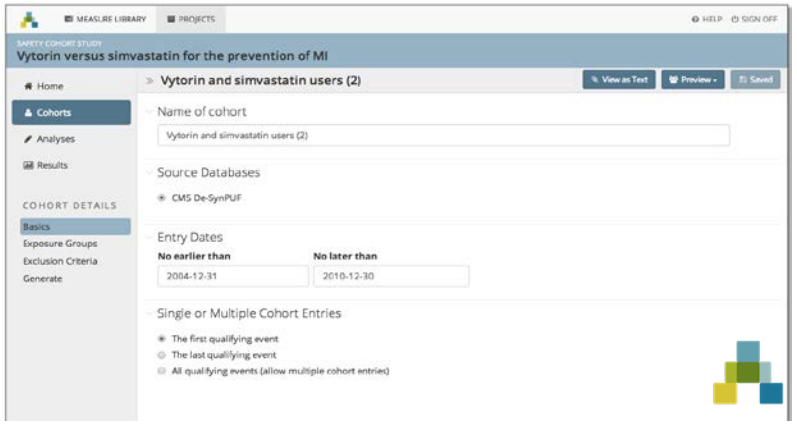
7. Use validated RWE software platform [1)]
   a) Avoids design flaws
   b) Increased transparency
   c) Stores audit trails

1) Franklin et al. Epidemiology 2014

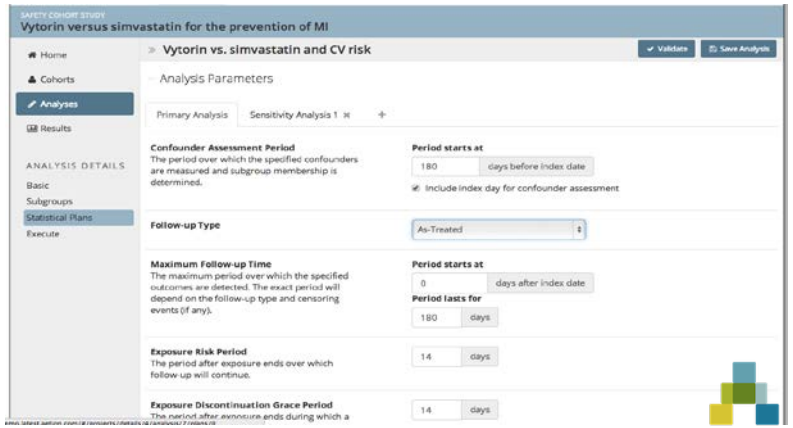
Structured user interfaces guide the user through the process collecting all study parameters



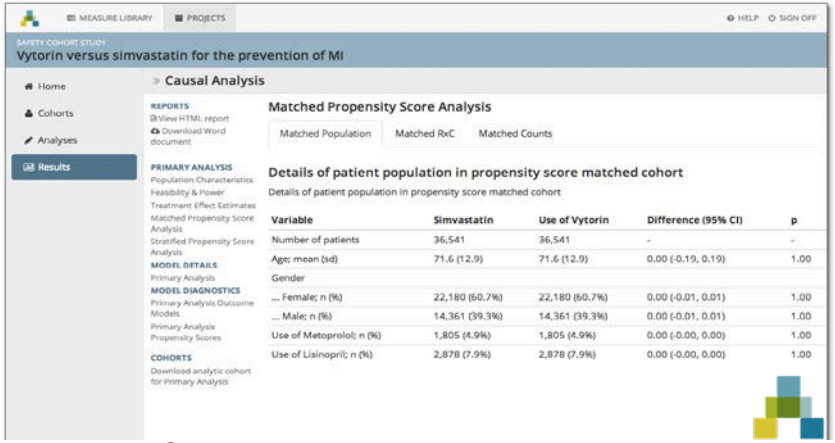
Select patients in transparent and reproducible ways



Select comparison group



Select follow-up model



Select risk adjustment

Analytic tools are build for 100% transparency

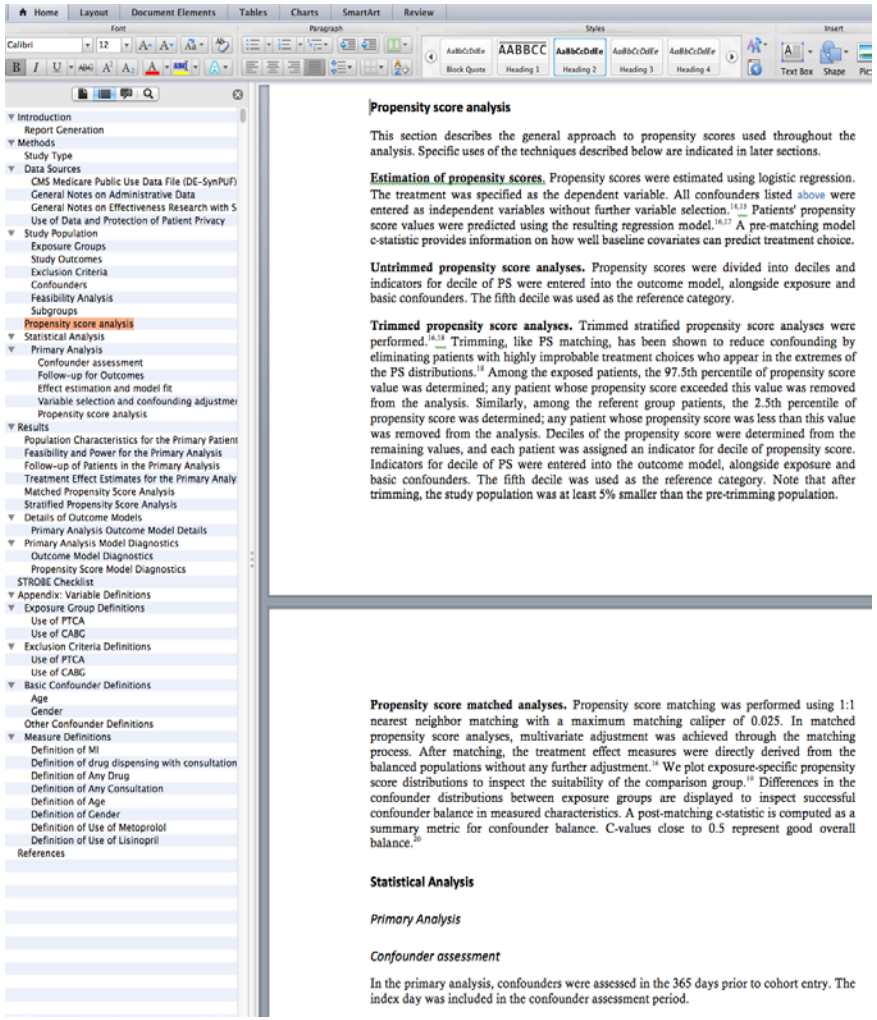
Tabular format (FDA Sentinel)

Enrollment Gap: 45 days
Age Groups: 18+
Query Period: 1/1/2008 to all data available as of sent date
Coverage Requirement: Medical and Drug Coverage
Enrollment Requirement: 183 days

		Run 1		R
		Exposure of Interest Glyburide	**Comparator of Interest** Glipizide	**Exposure of Interest** Glyburide
Drug/ Exposure:	Incident w/ respect to:	Glyburide, glipizide and other secretagogues including chlorpropamide, tolbutamide, tolazamide, glimepiride, nateglinide, repaglinide, acetohexamide	Glipizide, glyburide, and other secretagogues including chlorpropamide, tolbutamide, tolazamide, glimepiride, nateglinide, repaglinide, acetohexamide	Glyburide, glipizide and other secretagogues including chlorpropamide, tolbutamide, tolazamide, glimepiride, nateglinide, repaglinide, acetohexamide
	Washout (days)	183	183	183
	Cohort Definition	01	01	01
	Episode Gap	14	14	14
	Exposure Extension Period	14	14	14
	Minimum Episode Duration	0	0	0
	Minimum Days Supplied	0	0	0
	Induction Period	0	0	0
	Truncation by Death	Yes	Yes	Yes
	Episode Truncation by Incident Exposure	Yes	Yes	Yes
Event/ Outcome:	Event/ Outcome	Hypoglycemia (See event algorithm)	Hypoglycemia (See event algorithm)	Hypoglycemia (See event algorithm)
	Care Setting/PDX	ED* or IPP	ED* or IPP	ED*
	Incident w/ respect to:	Hypoglycemia (See event algorithm)	Hypoglycemia (See event algorithm)	Hypoglycemia (See event algorithm)
	Washout (days)	30	30	30
Propensity Score Match (PSM) Analysis:	PSM Ratio	1:1		1
	PSM Caliper	0.025		0.
	Covariate evaluation window (days)	183		1
	Perform HDPS Analysis	Yes		Y
	Number of covariates considered for each claim type	100		1
	Number of covariates kept from pool of considered covariates	200		2
	Covariate selection method	Exposure association-based selection		Exposure associat
	Zero Cell Correction	Yes		Y

National Drug Codes (NDCs) checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
HCPCS codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight

Text and tabular format AETION



One Off Line programming in RWD analyses (SAS, Stata, R etc.)

Line programming against line programming (double programming, same protocol):

- 10+ examples at BWH
- In 100% get different findings!

Line programming against FDA Sentinel tools:

- 3 examples at BWH
- In 100% there were errors in line programming

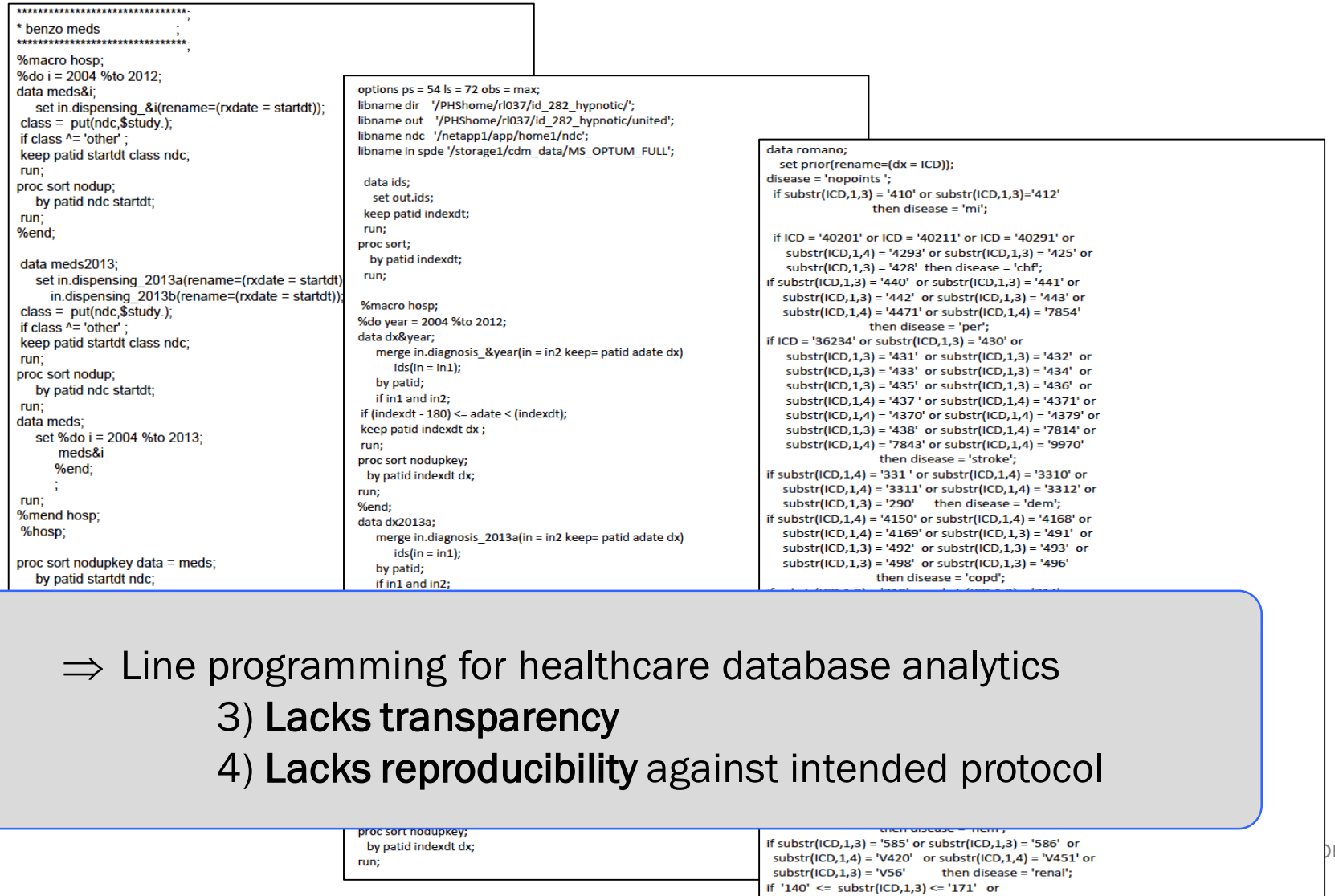
Line programming against Aetion platform:

- More than 50 validation activities in >20 organizations
- In 100% of activities there were errors in line programming
  - 70% misinterpretation or alternative assumption
  - 30% coding errors (time related, definitions)

⇒ Line programming for healthcare database analytics is
1) **Inherently error prone**
2) **Not validatable at scale**

Sharing programming code is not helpful…

… as it does not clarify whether the indented study was implemented accurately



```
**********************************;
* benzo meds                     ;
**********************************;
%macro hosp;
%do i = 2004 %to 2012;
data meds&i;
    set in.dispensing_&i(rename=(rxdate = startdt));
 class =  put(ndc,$study.);
 if class ^= 'other' ;
 keep patid startdt class ndc;
 run;
proc sort nodup;
    by patid ndc startdt;
 run;
%end;

 data meds2013;
    set in.dispensing_2013a(rename=(rxdate = startdt)
        in.dispensing_2013b(rename=(rxdate = startdt));
 class =  put(ndc,$study.);
 if class ^= 'other' ;
 keep patid startdt class ndc;
 run;
proc sort nodup;
    by patid ndc startdt;
 run;
data meds;
    set %do i = 2004 %to 2013;
         meds&i
        %end;
        ;
 run;
%mend hosp;
 %hosp;

proc sort nodupkey data = meds;
    by patid startdt ndc;
```

```
options ps = 54 ls = 72 obs = max;
libname dir   '/PHShome/rl037/id_282_hypnotic/';
libname out   '/PHShome/rl037/id_282_hypnotic/united';
libname ndc   '/netapp1/app/home1/ndc';
libname in spde '/storage1/cdm_data/MS_OPTUM_FULL';

 data ids;
   set out.ids;
 keep patid indexdt;
 run;
proc sort;
   by patid indexdt;
 run;

 %macro hosp;
%do year = 2004 %to 2012;
data dx&year;
    merge in.diagnosis_&year(in = in2 keep= patid adate dx)
        ids(in = in1);
    by patid;
    if in1 and in2;
 if (indexdt - 180) <= adate < (indexdt);
 keep patid indexdt dx ;
 run;
proc sort nodupkey;
  by patid indexdt dx;
run;
%end;
data dx2013a;
    merge in.diagnosis_2013a(in = in2 keep= patid adate dx)
        ids(in = in1);
    by patid;
    if in1 and in2;
```

```
data romano;
   set prior(rename=(dx = ICD));
disease = 'nopoints ';
  if substr(ICD,1,3) = '410' or substr(ICD,1,3)='412'
                then disease = 'mi';

  if ICD = '40201' or ICD = '40211' or ICD = '40291' or
     substr(ICD,1,4) = '4293' or substr(ICD,1,3) = '425' or
     substr(ICD,1,3) = '428'  then disease = 'chf';
if substr(ICD,1,3) = '440'  or substr(ICD,1,3) = '441' or
    substr(ICD,1,3) = '442'  or substr(ICD,1,3) = '443' or
    substr(ICD,1,4) = '4471' or substr(ICD,1,4) = '7854'
                then disease = 'per';
if ICD = '36234' or substr(ICD,1,3) = '430' or
     substr(ICD,1,3) = '431'  or substr(ICD,1,3) = '432'  or
     substr(ICD,1,3) = '433'  or substr(ICD,1,3) = '434'  or
     substr(ICD,1,3) = '435'  or substr(ICD,1,3) = '436'  or
     substr(ICD,1,4) = '437 ' or substr(ICD,1,4) = '4371' or
     substr(ICD,1,4) = '4370' or substr(ICD,1,4) = '4379' or
     substr(ICD,1,3) = '438'  or substr(ICD,1,4) = '7814' or
     substr(ICD,1,4) = '7843' or substr(ICD,1,4) = '9970'
                then disease = 'stroke';
if substr(ICD,1,4) = '331 ' or substr(ICD,1,4) = '3310' or
    substr(ICD,1,4) = '3311' or substr(ICD,1,4) = '3312' or
    substr(ICD,1,3) = '290'      then disease = 'dem';
if substr(ICD,1,4) = '4150' or substr(ICD,1,4) = '4168' or
    substr(ICD,1,4) = '4169' or substr(ICD,1,3) = '491'  or
    substr(ICD,1,3) = '492'  or substr(ICD,1,3) = '493'  or
    substr(ICD,1,3) = '498'  or substr(ICD,1,3) = '496'
                then disease = 'copd';
```

```
proc sort nodupkey;
  by patid indexdt dx;
run;
```

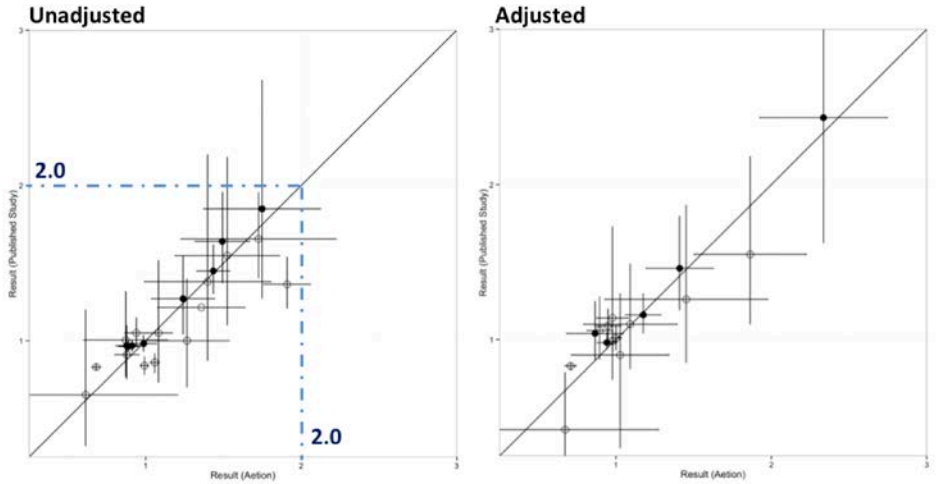
```
if substr(ICD,1,3) = '585' or substr(ICD,1,3) = '586'  or
  substr(ICD,1,4) = 'V420'   or substr(ICD,1,4) = 'V451' or
  substr(ICD,1,3) = 'V56'          then disease = 'renal';
if '140' <=  substr(ICD,1,3) <= '171'   or
```

⇒ Line programming for healthcare database analytics

3) **Lacks transparency**

4) **Lacks reproducibility** against intended protocol

Lack of reporting details make RWD studies non-reproducible



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

100

18

32

SV Wang[1], P Verpillat[2], JA Ras[illegible]A Patrick[illegible]rry[4] an[illegible]els[2,5]

The scientific community and decision-[illegible]kers ar[illegible]creasingly [illegible]ce[illegible] about tra[illegible]arency and reproducibility of epidemiologic studies using longitudinal hea[illegible]are da[illegible]ses. We ex[illegible]re[illegible]e extent to[illegible]ch published pharmacoepidemiologic studies using commercially availa[illegible]databa[illegible]could be r[illegible]odu[illegible]d by other i[illegible]stigators. We identified a nonsystematic sample of 38 descriptive[illegible]compar[illegible]e safety[illegible]ectiv[illegible]s coho[illegible]udies. Seven studies were excluded from reproduction, five because [illegible]dar[illegible]gn princip[illegible]o because of grossly inadequate reporting. In the remaining studies, >1,000 patient characteristics and measures of association were reproduced with a high degree of accuracy (median differences between original and reproduction <2% and <0.1). An essential component of transparent and reproducible research with healthcare databases is more complete reporting of study implementation. Once reproducibility is achieved, the conversation can be elevated to assess whether suboptimal design choices led to avoidable bias and whether findings are replicable in other data sources.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The scientific community and decision-makers are increasingly concerned about transparency and reproducibility of biomedical science.

WHAT QUESTION DID THIS STUDY A[illegible]SS?

☑ Recent high profile efforts to reproduce [illegible]ni[illegible]and clinical studies have drawn attention to this issue; ho[illegible]er, there has not yet been a large-scale effort to evaluate re[illegible]ducibility of healthcare database studies.

WHAT THIS STUDY ADDS TO OUR KNO[illegible]EDGE

☑ With sufficient transparency in reporti[illegible]a-base studies can be reproduced with great accuracy; however, there is great variability in the degree to which recently published healthcare database studies are reproducible. The reproduction team made informed guesses in >50% of reproduced studies, highlighting the need for greater transparency in

[illegible]OW [illegible]HIS MIGHT CHANGE CLINICAL [illegible]PHARM[illegible]OLOGY AND THERAPEUTICS

[illegible]reporting of key design choices and codes used to [illegible]the analytic population are a necessary component [illegible]or repro[illegible]ility of healthcare database studies. Barriers to [illegible]reproducib[illegible]can be outlined and quantified, paving the way [illegible]improvement with implementation of measures [illegible]designed to incentivize changes in research culture and practice.

Concerns about reproducibility of biomedical science have moved funding agencies, professional research societies, and journal editors to strengthen the transparency of the research process in preclinical, clinical, and population health sciences.[1–3] Transparency and reproducibility are intertwined concepts. There is general agreement that transparency can be achieved through a series of such measures as: (1) registration of study protocols before the initiation of research to increase the chance that all study results will become publicly available; (2) reporting guidelines to encourage complete description of all details necessary to reproduce study findings; and (3) making the a[illegible]h data available to other researchers to reproduce f[illegible]gs or ma[illegible]ddi-tional discoveries.[4–7] Funding agencies, such as the National Institutes of Health and the Patient Centered Outcomes Research Institute, have made public statements about the necessity to make research data available for reproduction by independent research groups.[8,9]

Randomized clinical trials are at the forefront of activities to increase transparency and reproducibility. Regulatory agencies and journal editors require the registration of clinical trial protocols,[10] and observational studies are increasingly encouraged to follow suit.[4,11,12] Randomized clinical trials have extensive guidelines and [illegible]ith regard to design, conduct, and reporting.[13,14] After consort[illegible]of pharmaceutical companies in the United States

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, [illegible]Medical/Brigham & W[illegible]'s Hospital, Boston, Massachusetts, USA; [2]Corporate Department Global Epidemiology, Boehringer Ingelheim, I[illegible]many; [3]Aetion, Inc.[illegible]York, New York, USA; [4]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [5][illegible]er Medical Sc[illegible]Hannover, Germany. Correspondence: SV Wang (swang27@partners.org)

Received 23 September 2015; accepted 4 December 2015[illegible]ce online p[illegible]ion 21[illegible]ber 2015. doi:10.1002/cpt.329

Wang et al. CP&T 2016

Quantify the current state of reproducibility of database studies

Systematic search using Google Scholar

Include descriptive or comparative safety/effectiveness cohort studies

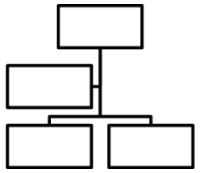
Randomly sample **250 studies**

Consider all publically available information

Replicate studies
(blind to original results)

Contact original authors to under-stand assumptions, differences

Top h-5 clinical, epidemiology journals
- **Published after Jan 1, 2011**
- **"cohort" + "claims" + database name**



CONSORT style diagram
- **Exclude if data source mismatch or PDF unavailable**

- **Standardized extraction form**

Metrics to quantify reproducibility
Frequency insufficient reporting, Std. Diff, etc.





Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

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on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making

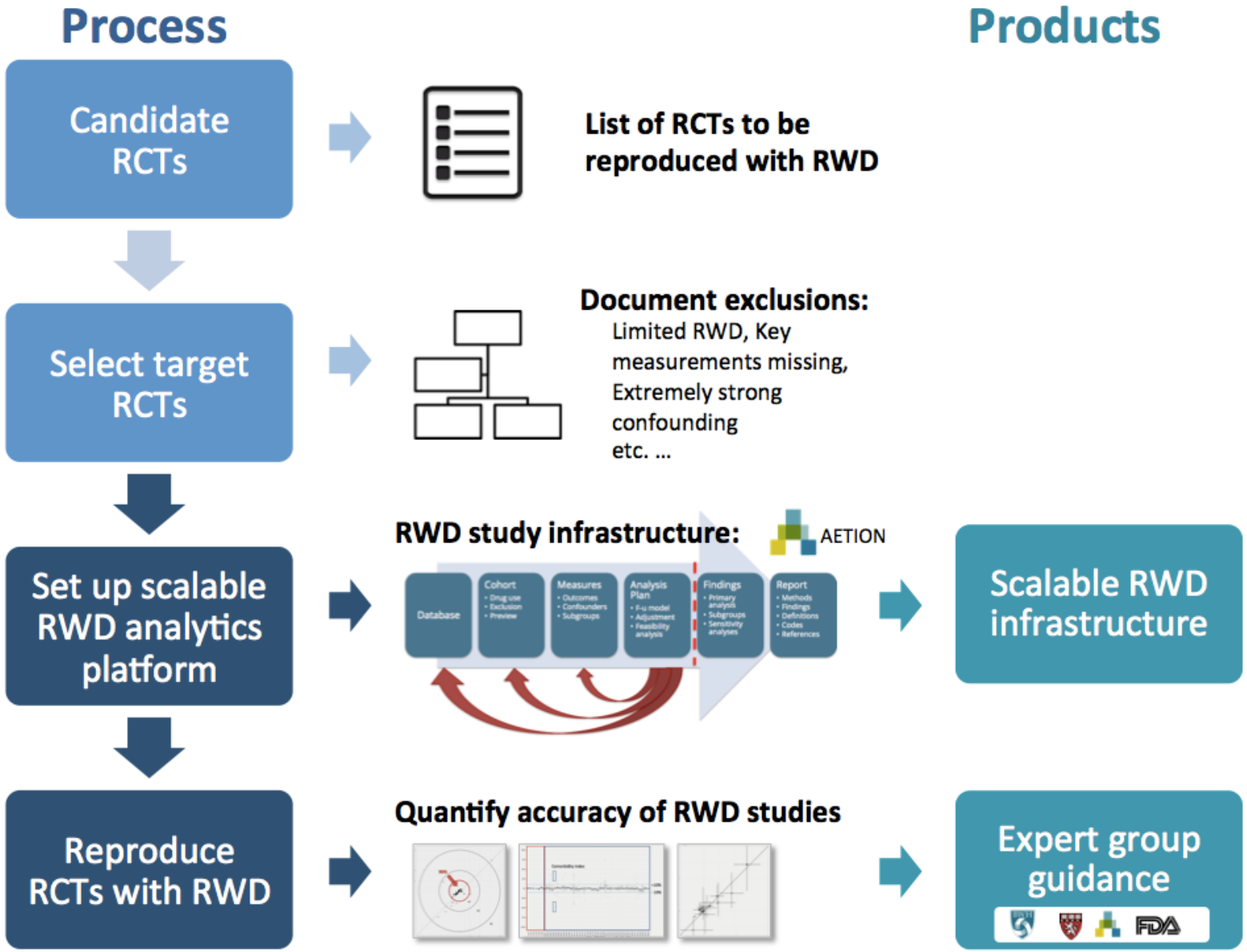
International Society for Pharmacoepidemiology

International Society for Pharmacoeconomics and Outcomes Research

TABLE 2 Reporting specific parameters to increase reproducibility of database studies*

	Description	Example	Synonyms
A. Reporting on data source should include:			
A.1 Data provider	Data source name and name of organization that provided data.	Medicaid Analytic Extracts data covering 50	
A.2 Data extraction date (DED)	The date (or version number) wh extracted from the dynamic ra data stream (e.g. date that the for research use by the vendo		
A.3 Data sampling	The search/extraction criteria ap source data accessible to the r subset of the data available fro		
A.4 Source data range (SDR)	The calendar time range of data study. Note that the implemen use only a subset of the availa		
D. Reporting on exposure definition should include:			
D.1 Type of exposure	The type of exposure that is captured or measured, e.g. drug versus procedure, new use, incident, prevalent, cumulative, time-varying.	We evaluated risk of outcome Z following incident exposure to drug X or drug Y. Incident exposure was defined as beginning on the day of the first dispensation for one of these drugs after at least 180 days without dispensations for either (SED). Patients with incident exposure to both drug X and drug Y on the same SED were excluded. The exposure risk window for patients with Drug X and Drug Y began 10 days after incident exposure and continued until 14 days past the last days supply, including refills. If a patient refilled early, the date of the early refill and subsequent refills were adjusted so that the full days supply from the initial dispensation was counted before the days supply from the next dispensation was tallied. Gaps of less than or equal to 14 days in between one dispensation plus days supply and the next dispensation for the same drug were bridged (i.e. the time was	
D.2 Exposure risk window (ERW)	The ERW is specific to an exposure and the outcome under investigation. For drug exposures, it is equivalent to the time between the minimum and maximum hypothesized induction time following ingestion of the molecule.		Drug era, risk window
D.2a Induction period[1]	Days on or following study entry date during which an outcome would not be counted as "exposed time" or "comparator time".		Blackout period
D.2b Stockpiling[1]	The algorithm applied to handle leftover days supply if there are early refills.		
D.2c Bridging exposure episodes[1]	The algorithm applied to handle gaps that are longer than expected if there was perfect adherence (e.g. non-overlapping dispensation + day's supply).		Episode gap, grace period, persistence window, gap days

How well can RWD analyses reproduce RCT findings?



RWE fit for Decision Making in Healthcare

MVET framework for RWE that is fit for DM

CP&T 2016;100:633-46

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]

ISPE/ISPOR consensus paper on reproducibility

Pharmacoepi Drug Saf 2017;9:1018-32

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When and how to augment RCTs with RWE

CP&T 2017;102:924-33

When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials?

Jessica M. Franklin[1] and Sebastian Schneeweiss[1]

A pathway