Healthcare databases and Public Health

Effectiveness Research with longitudinal healthcare databases

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SISMEC, Pavia, Italy

Agenda

- Comparative Effectiveness Research (CER) with healthcare databases as a strategy to improve Public Health
- Three examples of effectiveness research leveraging different healthcare databases
- Near-real-time monitoring of new medical products for timely effectiveness information

Motivation for CER

- Relative absence of studies that directly compare available treatment options
  - Vs. large number of placebo controlled efficacy trials
- Based on belief that better decisions on the use of resources improve the public's health and reduce costs of care, US Congress allocated substantial amounts to CER
  - 2009: Stimulus package (ARRA): $1.1 bln for CER
  - 2010: Affordable care act (PPACA) created PCORI and allocated $3 bln over the next decade to fund CER

Source: http://www.hsph.harvard.edu/comparative-effectiveness-research-initiative/resources-and-links/funding-sources/

CER in words

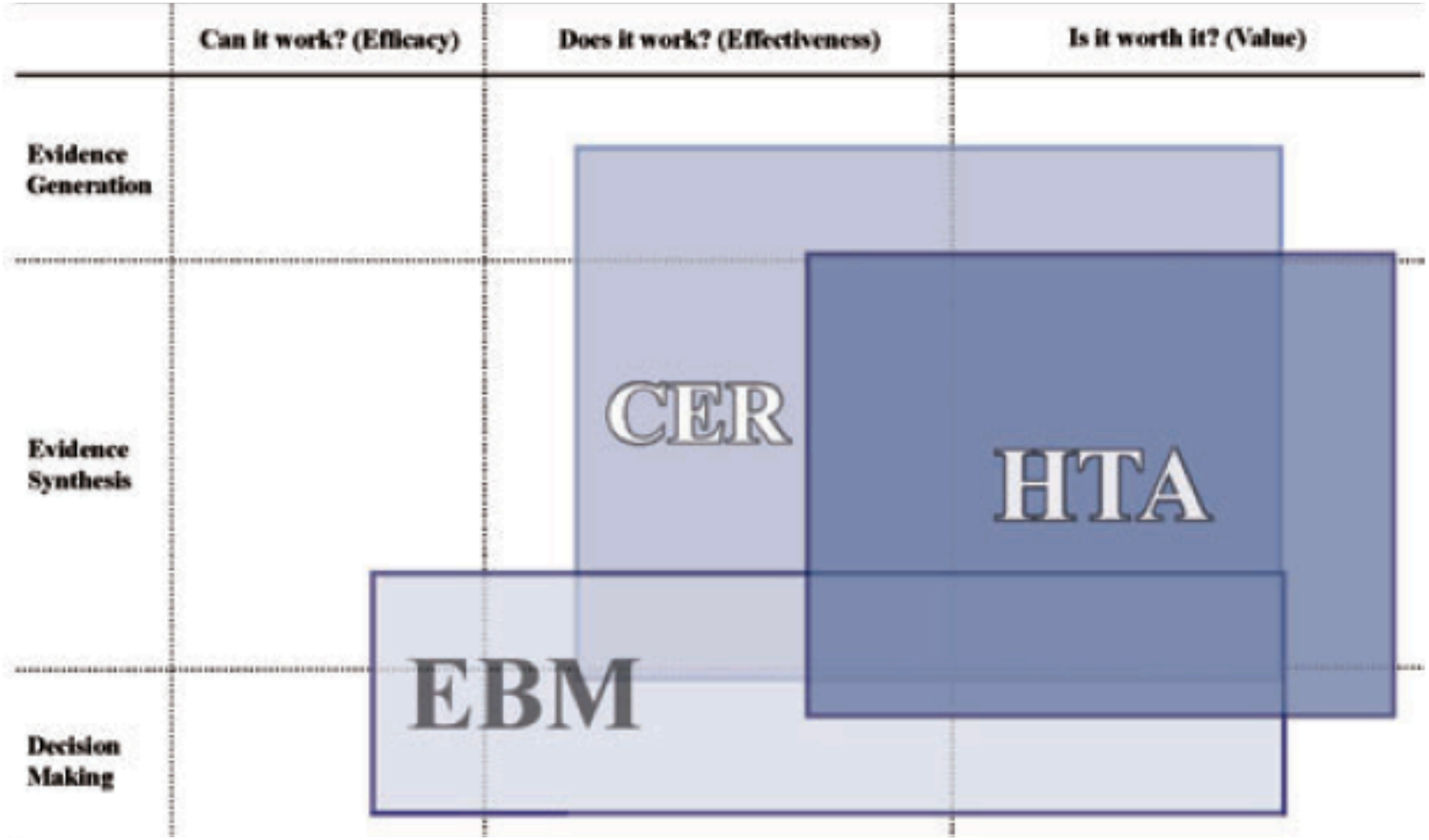
- Promotes studies comparing the **effectiveness and safety** of alternative ways of addressing common clinical problems in a "real world setting".
- Interventions to be evaluated include pharmaceuticals, devices, procedures, and diagnostic approaches.
- The ultimate goal is to support optimal decision-making by stakeholders in the healthcare system, including patients, physicians, provider organizations, etc.

(AHRQ)

CER and its cousins

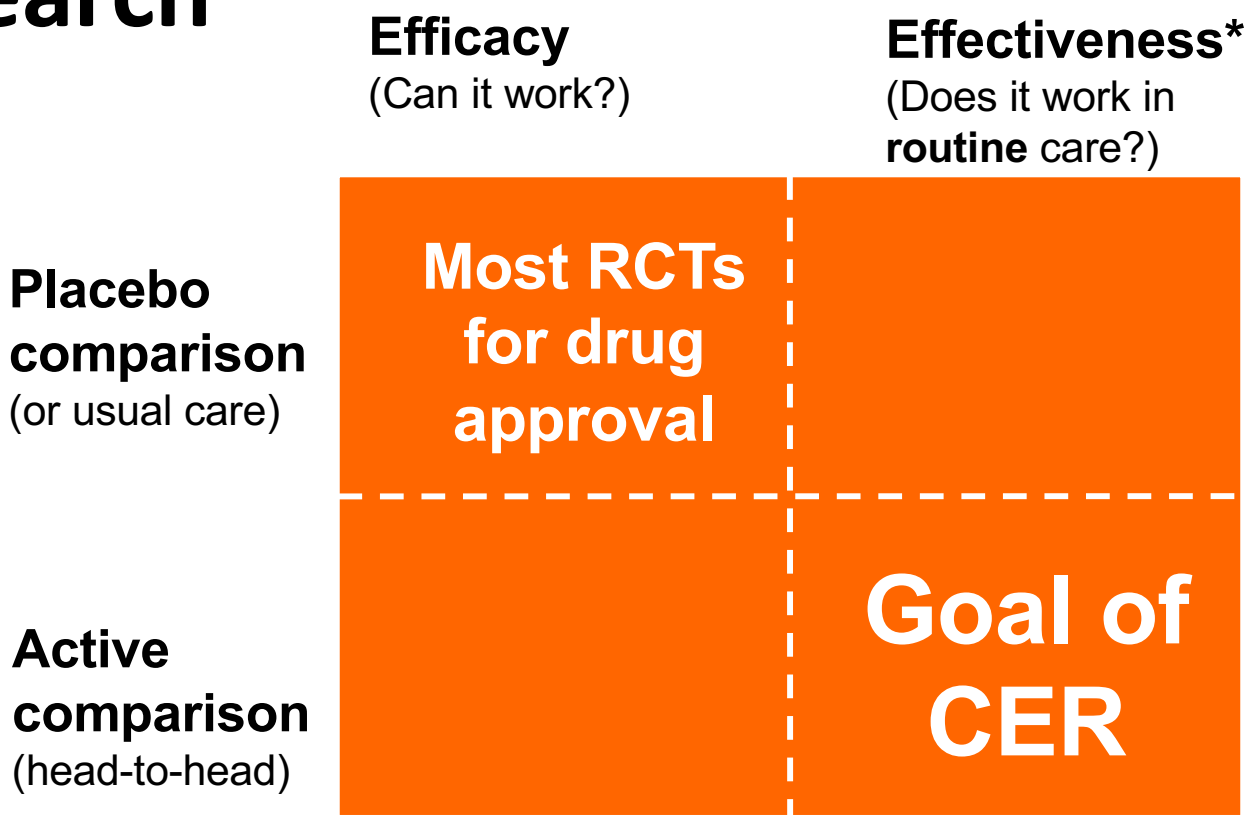
Evidence questions

Function



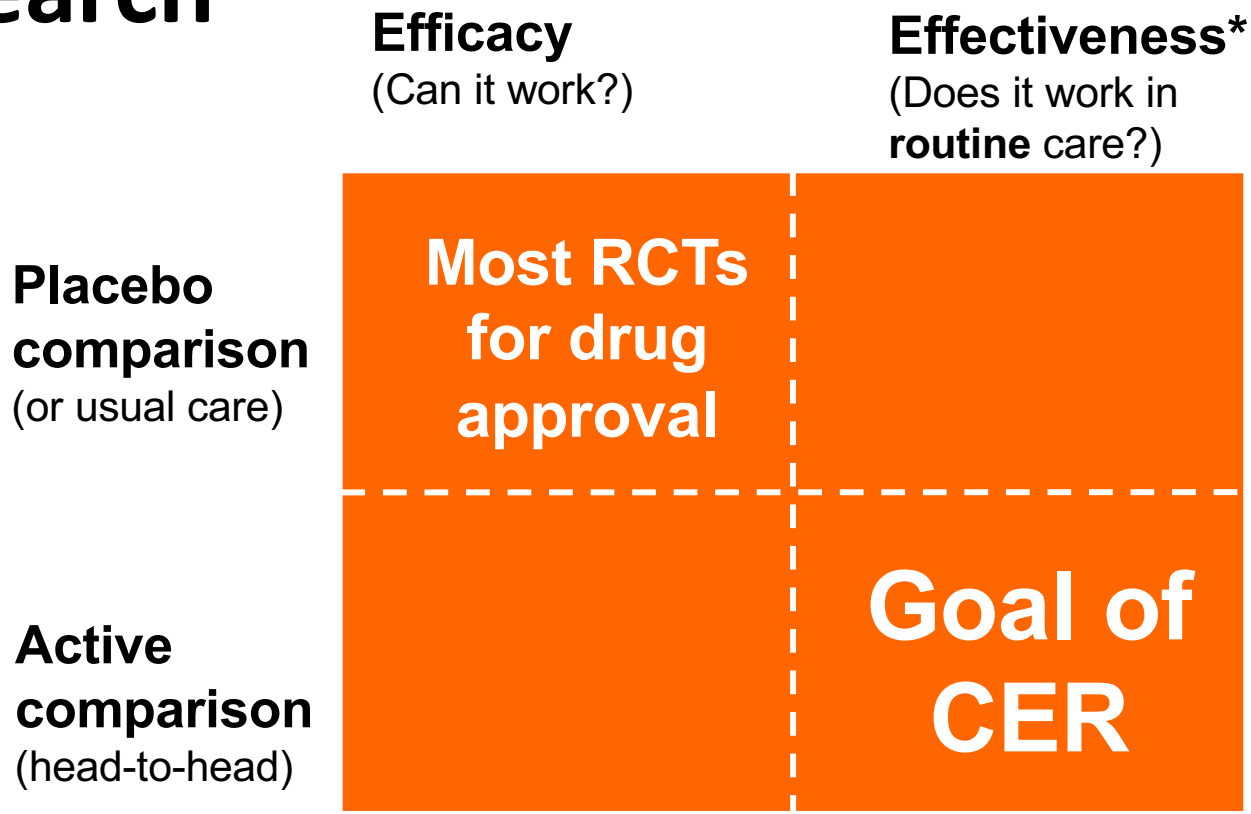
Luce et al. The Milbank Quarterly. 2010

Objective of Comparative Effectiveness Research



* Cochrane A. Nuffield Provincial Trust, 1972

Objective of Comparative Effectiveness Research



Effectiveness = Efficacy X Adherence X Subgroup effects (+/-)

RCT

Reality of routine care

* Cochrane A. Nuffield Provincial Trust, 1972

As much as we all love randomized trials…

- It is an unrealistic expectation that we will have head-to-head randomized trials
  - for every intervention and
  - its combinations
  - in every patient subgroup
  - that exactly mimic routine care
- Randomized studies may take some time to conduct
  - We need effectiveness evidence in a timely manner

Limitations of clinical trial data

- Under-representation of some populations
  - Esp. the elderly, the complex, and the young
- Small number of subjects
- All-volunteer patients
- Atypical clinicians, settings
- Protocolized care: compliance, monitoring
- Outcome often is a surrogate measure
- Comparator is often placebo
- Short duration

Limitations of clinical trial data

What if adverse event:

- Affects 1 in 500 patients?
- Takes 2 years to develop?
- Occurs primarily
  - in the elderly, children, pregnant women?
  - with the concurrent use of another drug?
  - in the presence of a particular co-existing disease?

Observational CER with Electronic Healthcare Data

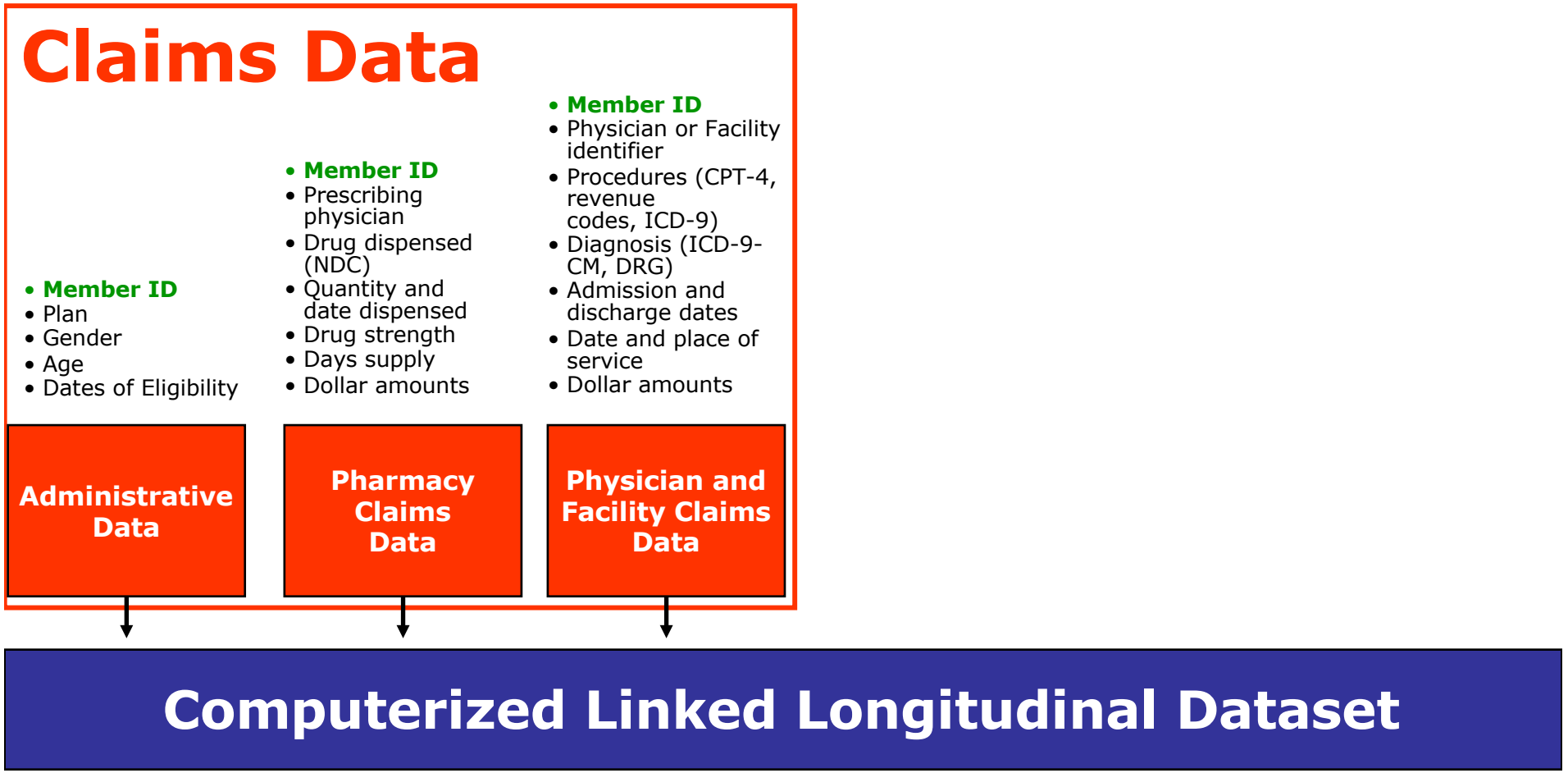
- Representative of routine care
  - Spectrum of disease severity
  - Spectrum of co-morbidities
  - Co-medications
  - Real world adherence
- Very large size
  - Can study rare outcomes
  - Infrequent exposure, recently marketed medications
  - Many subgroups to study treatment effect heterogeneity
- Long follow-up
  - With hard clinical endpoints
- Produce results fast at low cost

Large healthcare databases

- Automated electronic recording of filled prescriptions, professional services, hospitalizations
- Collected routinely for payment and administration of health services
- Enormous growth in use
- Representative and complete for large patient populations, including the elderly, children, the very poor, nursing home patients

US Electronic healthcare data

- **Constant flow of data with little delay and at low cost**
- **Millions of patients with defined person–time denominator**
- **Data reflect routine care**
- **Generalizable to large population segments**
- **HIPAA compliance protects patient privacy**



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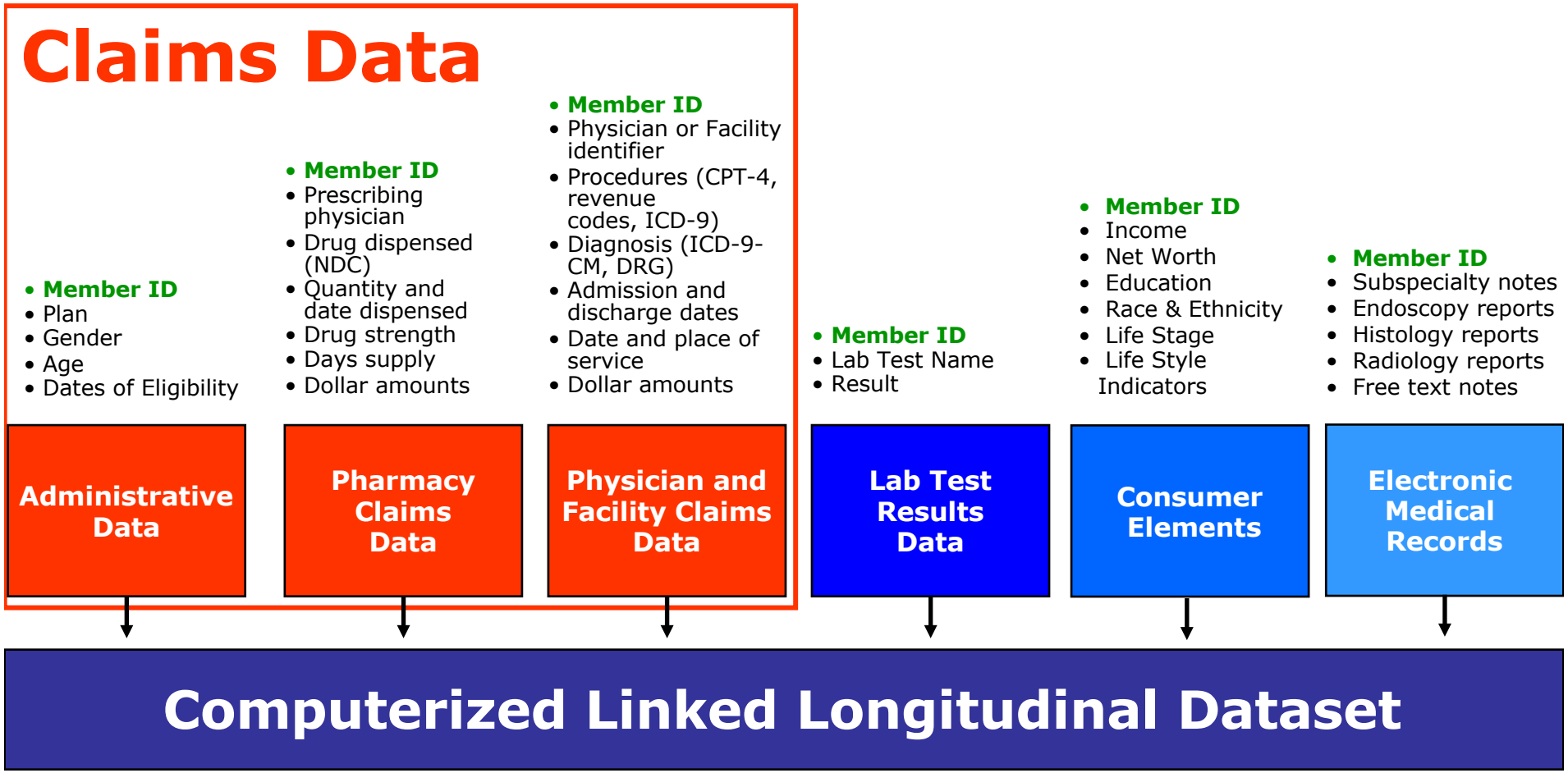
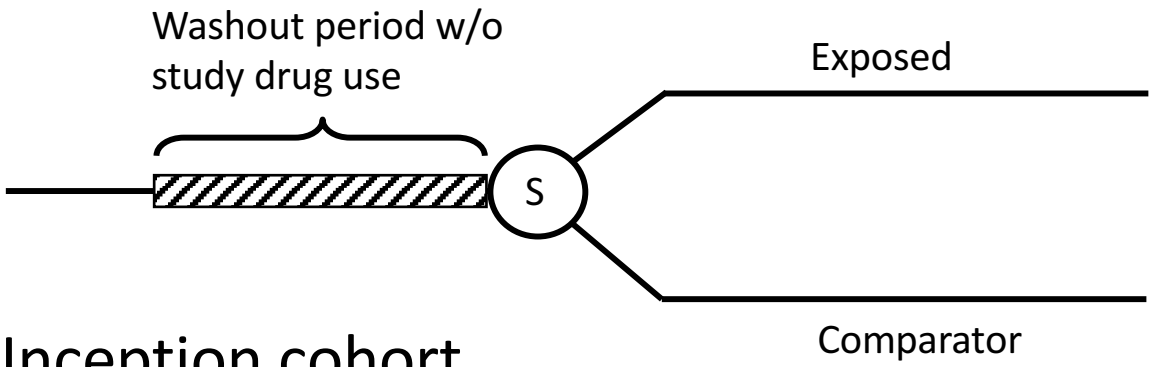
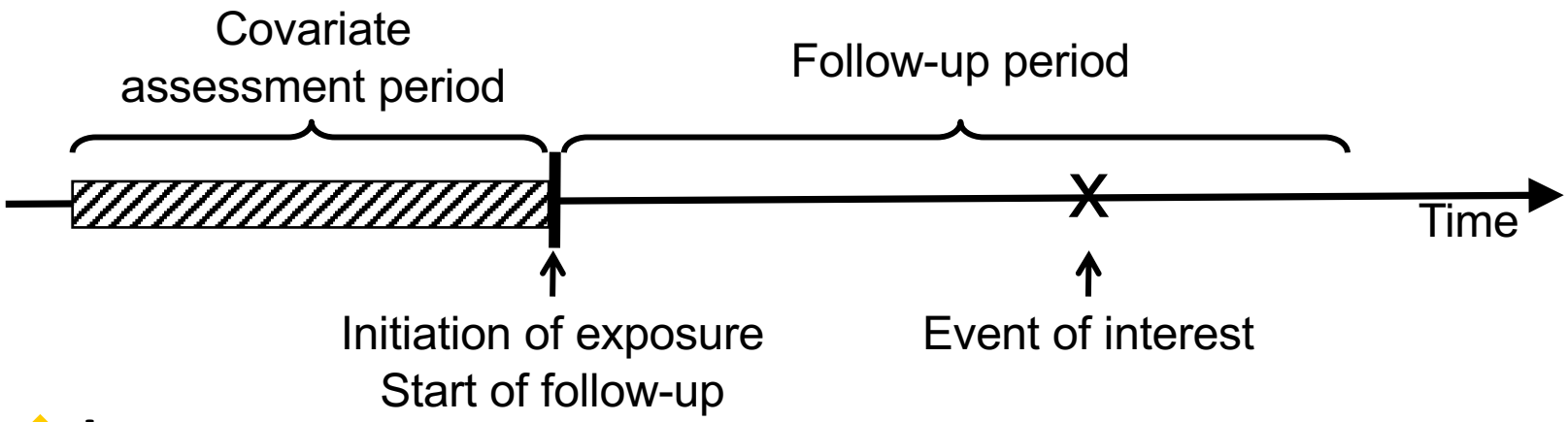


The Incident User Design



- Inception cohort
- Confounders measured before first exposure
- Allows to describe time-varying hazards
- Also reduces the risk for immortal time bias because exposure status is assessed before follow-up
- Its clarity provides less opportunity for mistakes
- Directly applicable for propensity score analysis

Basic design for CER



- **Inputs:**
  - Drug(s) and comparator(s) of interest
  - Timing and duration of exposure risk window and definition of exposure status within window (e.g., first exposure carried forward, as-treated)
  - Outcome of interest definition
  - Covariate definitions and duration of baseline assessment period
  - Confounding adjustment strategy

3 examples of effectiveness research leveraging different data sources

original article

Diabetes, Obesity and Metabolism 2016.

Comparative cardiovascular safety of glucagon-like peptide-1 receptor agonists versus other antidiabetic drugs in routine care: a cohort study

E. Patorno[1], B. M. Everett[2], A. B. Goldfine[3], R. J. Glynn[1], J. Liu[1], C. Gopalakrishnan[1] & S. C. Kim[1,4]

[1] *Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[2] *Divisions of Cardiovascular and Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[3] *Clinical Research, Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA*
[4] *Division of Rheumatology, Allergy and Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

Aims: To evaluate the comparative cardiovascular disease (CVD) safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in head-to-head comparisons with dipeptidyl peptidase-4 (DPP-4) inhibitors, sulphonylureas or insulin, when added to metformin, as used in 'real-world' patients with type 2 diabetes mellitus (T2DM).

Methods: Within a large US commercial health plan database linked to laboratory test results, we identified three pairwise 1 : 1 propensity-score-matched cohorts of patients with T2DM aged ≥18 years treated with metformin who initiated a GLP-1 RA or a comparator, i.e. DPP-4 inhibitor (n = 35 534), second-generation sulphonylureas (n = 28 138) or insulin (n = 47 068), between 2005 and 2013. We examined the association between drug initiation and a composite CVD endpoint, comprising hospitalizations for acute myocardial infarction, unstable angina, stroke or coronary revascularization.

Results: During the course of 1 year, there were 13.9 and 13.7 CVD events per 1000 person-years among propensity-score-matched initiators of GLP-1 RAs versus DPP-4 inhibitors [hazard ratio (HR) 1.02; 95% confidence interval (CI) 0.84–1.24]; and 12.1 versus 14.0 events among initiators of GLP-1 RAs versus sulphonylureas (HR 0.86; 95% CI 0.69–1.08). The effect estimates for GLP-1 RAs versus insulin were sensitive to the adjustment for glycated haemoglobin, after which the HR was 1.01 (95% CI 0.73–1.41). Results were robust across several sensitivity analyses, including an as-treated analysis considering up to 8.7 years of follow-up.

Conclusions: This large study, performing head-to-head comparisons of GLP-1 RAs with other antidiabetic agents in real-world patients, provides estimates of relative safety precise enough to exclude large differences in CVD risk and adds further understanding to results from recent clinical trials.

original article

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[2] *Divisions of*
[3] *Clinical Res*
[4] *Division of*

To evaluate the effect of GLP-1 RAs on the risk of CVD events compared with other antidiabetic agents as used in routine care using a large commercial insurance database (Optum/United)

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Data source

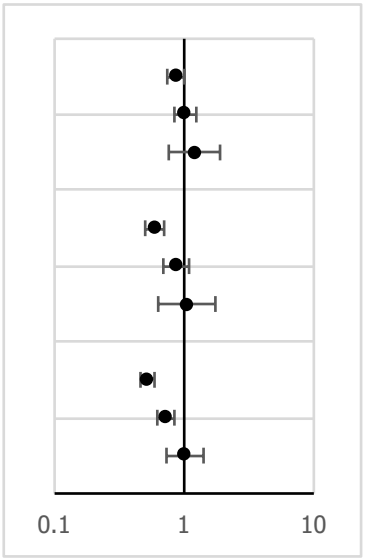
- Optum Clinformatics (UnitedHealth)
- Large commercial insurance database covering more than 14 million persons annually across the U.S. (Commercial + Medicare Advantage)
- Demographic information, inpatient and outpatient claims, filled prescriptions
- Data linked to laboratory test results for a subset of beneficiaries (HbA1c levels)

Study design

- Study participants: ≥18 years with T2DM initiating an antidiabetic agent
- Exposure drug: GLP-1 RAs
- Comparator drug: DPP-4 inhibitors, sulfonylureas, insulin
- Study period: Apr 2005 – Dec 2013
- Databases: Optum Clinformatics
- Outcome: CV composite outcome
- Patient follow-up: until 1 year or first of drug discontinuation/switch
- Analysis:
  - 1:1 PS-matching including over 80 baseline characteristics
  - Cox proportional hazards regression models

Risk of CVD endpoint

ANALYSIS	N	Cases	PYs	IR	N	Cases	PYs	IR	HR (95% CI)
	GLP-1 RA				DPP-4i				
Unadjusted	18,658	203	15,113	13.4	69,807	871	55,846	15.7	0.86 (0.74-1.00)
PS-matched	17,767	200	14,391	13.9	17,767	197	14,391	13.7	1.02 (0.84-1.24)
HbA1c-PS-matched	4,217	41	3,374	12.1	4,217	34	3,374	10.1	1.20 (0.76-1.89)
	GLP-1 RA				2nd gen SU				
Unadjusted	14,466	139	11,573	12.0	114,480	1840	90,439	20.4	0.59 (0.50-0.70)
PS-matched	14,069	136	11,255	12.1	14,069	154	10,974	14.0	0.86 (0.69-1.09)
HbA1c-PS-matched	3,534	31	2,792	11.0	3,534	29	2,757	10.5	1.05 (0.63-1.74)
	GLP-1 RA				Insulin				
Unadjusted	29,343	339	23,768	14.3	42,982	914	33,096	27.5	0.52 (0.46-0.59)
PS-matched	23,574	287	19,095	15.1	23,574	386	18,388	21.0	0.72 (0.62-0.84)
HbA1c-PS-matched	4,904	72	3,923	18.4	4,904	69	3,776	18.2	1.01 (0.73-1.41)



Conclusions

- This large study performing head-to-head comparisons of GLP-1 RA with other antidiabetic agents in real-world patients provides estimates of relative safety precise enough to exclude large differences in CVD risk.

BMJ

BMJ 2014;348:g4022 doi: 10.1136/bmj.g4022 (Published 27 June 2014)

RESEARCH

Comparative safety of anesthetic type for hip fracture surgery in adults: retrospective cohort study

Elisabetta Patorno *instructor*[1], Mark D Neuman *assistant professor*[2], Sebastian Schneeweiss *professor*[1], Helen Mogun *programmer*[1], Brian T Bateman *assistant professor*[1 3]

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BMJ

BMJ 2014;348:g4022 doi: 10.1136/bmj.g4022 (Published 27 June 2014)

RESEARCH

Com… surg…ure

Elisabe…

profess…

[1]Division o… School, Boston, MA… delphia, PA, USA; [3]

To investigate the effect of type of anesthesia on risk of in-hospital mortality using the largest nationwide database of inpatient hospital admissions in the US (Premier)

Premier

- National organization focused on healthcare performance improvement
- Data collected from member hospitals through Premier's informatics products
- Premier provides information to hospitals for benchmarking purposes
- **Premier Perspective Database**:
  - ~500 hospitals
  - 1/6th of all US admissions
  - Nationwide
  - Teaching and non-teaching hospitals
  - Urban and rural hospitals
  - All patients treated at these hospitals are included in the database, independent of payer status (Medicaid, Medicare, or commercial insurance).
  - **Profile of patients treated at hospitals participating in Premier is similar to those treated nationally**

Study design

- Study participants: ≥18 years discharged with a diagnosis of hip fracture and a surgical repair procedure
- Exposure drug: Regional anesthesia
- Comparator drug: General anesthesia
- Study period: Oct 2007 – Sept 2011
- Databases: Premier
- Outcome: In-hospital mortality
- Patient follow-up: until death or hospital discharge
- Analysis: Multivariable logistic model, mixed models to account for hospital variability

Main results and conclusions

Variables	General anesthesia	Regional anesthesia
No of patients	61 554	6939
No of in-hospital deaths	1362	144
Risk of in-hospital death (%)	2.2	2.1
Unadjusted analysis	Ref	0.94 (0.79 to 1.11)
Adjusted analysis*	Ref	0.93 (0.78 to 1.11)
Fully adjusted analysis†	Ref	0.93 (0.78 to 1.11)
Mixed effects analysis‡	Ref	0.91 (0.75 to 1.10)

- Mortality risk did not differ significantly by anesthesia type among patients undergoing hip fracture surgery.
- If the previously posited beneficial effect of regional anesthesia on short term mortality exists, it is likely to be more modest than previously reported.

Lithium Use in Pregnancy and the Risk of Cardiac Malformations

Elisabetta Patorno, MD DrPH[1]; Krista F. Huybrechts, MS PhD[1]; Brian T. Bateman, MD MSc[1,2]; Jacqueline M. Cohen, PhD[3]; Rishi J. Desai, PhD[1]; Helen Mogun, MS[1]; Lee S. Cohen, MD[4]; Sonia Hernandez-Diaz, MD DrPH[3]

1 Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

2 Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States

3 Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States

4 Center for Women's Mental Health, Massachusetts General Hospital, Boston, MA, United States

Currently under review

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1

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3

United States

4 Center for Women's Mental Health, Massachusetts General Hospital, Boston, MA, United States

To assess the risk of cardiac malformations associated with first trimester exposure to lithium using Medicaid data

Currently under review

Medicaid

- Before 1965
  - Incomplete health coverage for poor
- 1965: Social security amendments
  - Created Medicare and Medicaid
- Medicaid eligible population:
  - Aid to Families with Dependent Children recipients
  - Pregnant women (Medicaid covers medical care for > 40% births in the US)
  - Medically needy
- Now largest health insurer in US (with affordable care act)

Study design

- Study participants: pregnant women enrolled in Medicaid linked to live-born infants
- Exposure drug: Lithium use during 1st trimester (T1)
- Comparator: No use of lithium during T1
- Active comparator: Lamotrigine use during T1
- Study period: Jan 2000 – Dec 2010
- Databases: Medicaid Analytic eXtract (MAX)
- Outcome: Cardiac malformations
- Patient follow-up: until 3 months after delivery (babies)
- Analysis:
  - Fine stratification on PS including 50 baseline characteristics
  - Generalized linear models (PROC GENMOD with weight statement and loglink function)

Main results and conclusions

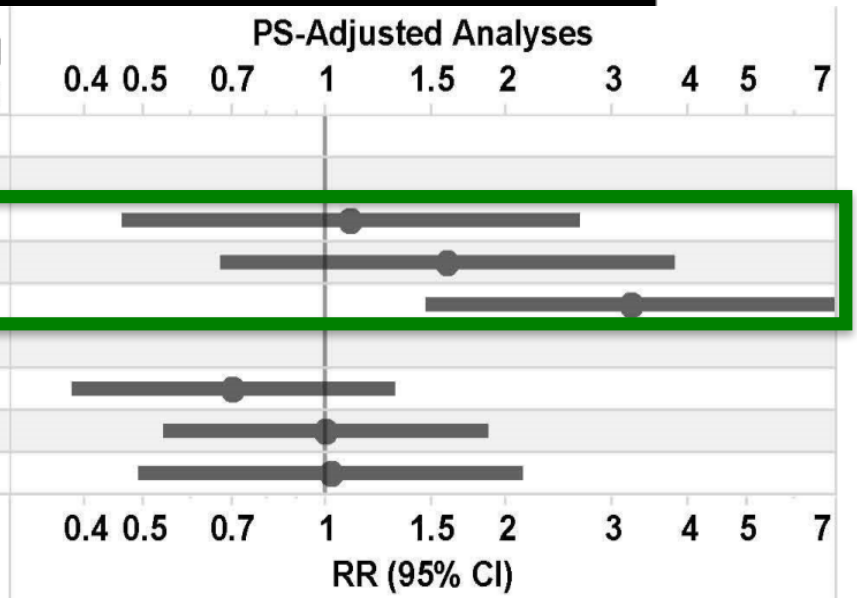
Exposure Group :	Unexposed	Lamotrigine	Lithium
Total	1322955	1945	663
Events	15251	27	16
Risk/1000 births	11.5	13.9	24.1
Unadjusted RR (95% CI)	Ref.	1.20 (0.83-1.75)	2.09 (1.29-3.40)
PS-adjusted RR (95% CI)	Ref.	0.89 (0.61-1.30)	1.65 (1.01-2.67)
PS-adjusted RR (95% CI)	.	Ref.	2.27 (1.19-4.34)

PS: propensity score; RR: risk ratios; CI: confidence intervals; Ref.: reference

- Maternal use of lithium during the first trimester is associated with a more modest increase in cardiac malformations than originally postulated.

Main results and conclusions

Exposure Group	Risk/1000 births	PS-adjusted RR (95% CI)
Unexposed	11.5	Ref.
Lithium (mg/day)		
≤600	16.4	1.10 (0.46-2.64)
601-900	21.3	1.59 (0.67-3.79)
>900	48.8	3.21 (1.47-6.99)
Lamotrigine (mg/day)		
≤100	11.1	0.70 (0.38-1.30)
101-200	16.1	1.00 (0.54-1.86)
>200	16.6	1.02 (0.49-2.12)



- Maternal use of lithium during the first trimester is associated with a more modest increase in cardiac malformations than originally postulated.
- Lithium's teratogenic effect on cardiac organogenesis might be dose dependent

Near-real-time monitoring of new medical products

All stakeholders need effectiveness information ASAP after marketing

- **Patient, provider:**
  - Need to know how much better/safer a new product is and in whom
  - for informed treatment choice, guideline updates
- **Manufacturer:**
  - Needs to demonstrate value compared to competitor
- **Payor:**
  - Needs to understand added effectiveness/safety for price negotiations, reimbursement level/ formulary position
- **Key decisions:**
  - In case of a superior new product:
    - ✓ Want to make sure it has fast uptake, provide early support for wide dissemination
  - In case of no added value/less effective:
    - ✓ Want to explore whether patient subgroups have added benefits
    - ✓ Want to avoid initial large-scale uptake; once use of a less effective product is established a trend is hard to reverse

Near-real-time monitoring

- Growing interest in establishing a national infrastructure system to enable near-real-time monitoring of new medical products within the routine care setting.
- These systems of networked databases can serve as national resources for rapid generation of CE evidence.
- The most prominent example in the U.S. is the FDA's Sentinel System

FDA's Sentinel Initiative *a brief history*

- 2007: FDAAA mandates FDA to establish active surveillance system for monitoring drugs using electronic healthcare data
- 2008: FDA establishes Sentinel Initiative which aims to develop and implement proactive system that will complement existing systems to track adverse events linked to medical products
- 2009-2014: FDA sponsors Mini-Sentinel pilot project to develop scientific operations for active medical product safety surveillance
- 2014-: Sentinel funded

Sentinel partner organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners

Sentinel Distributed Database

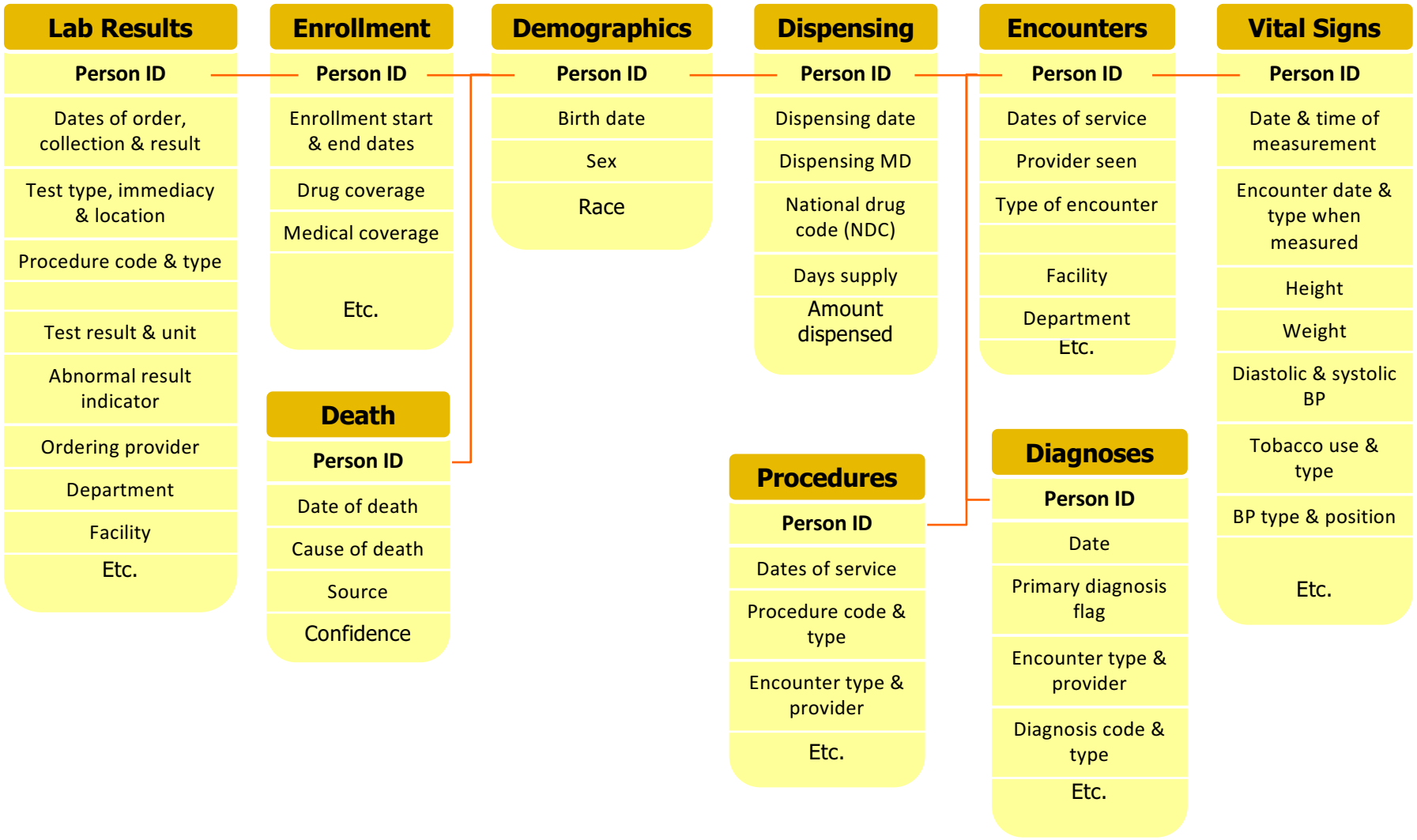
- **178 million** individuals*
  - **358 million** person-years of observation
- **4 billion** prescription drug dispensings
- **4.1billion** unique medical encounters
  - Including **42 million** inpatient stays
- Ability to obtain electronic or paper medical records

*As of September 2013. Potential for double-counting if individuals moved between Data Partner health plans

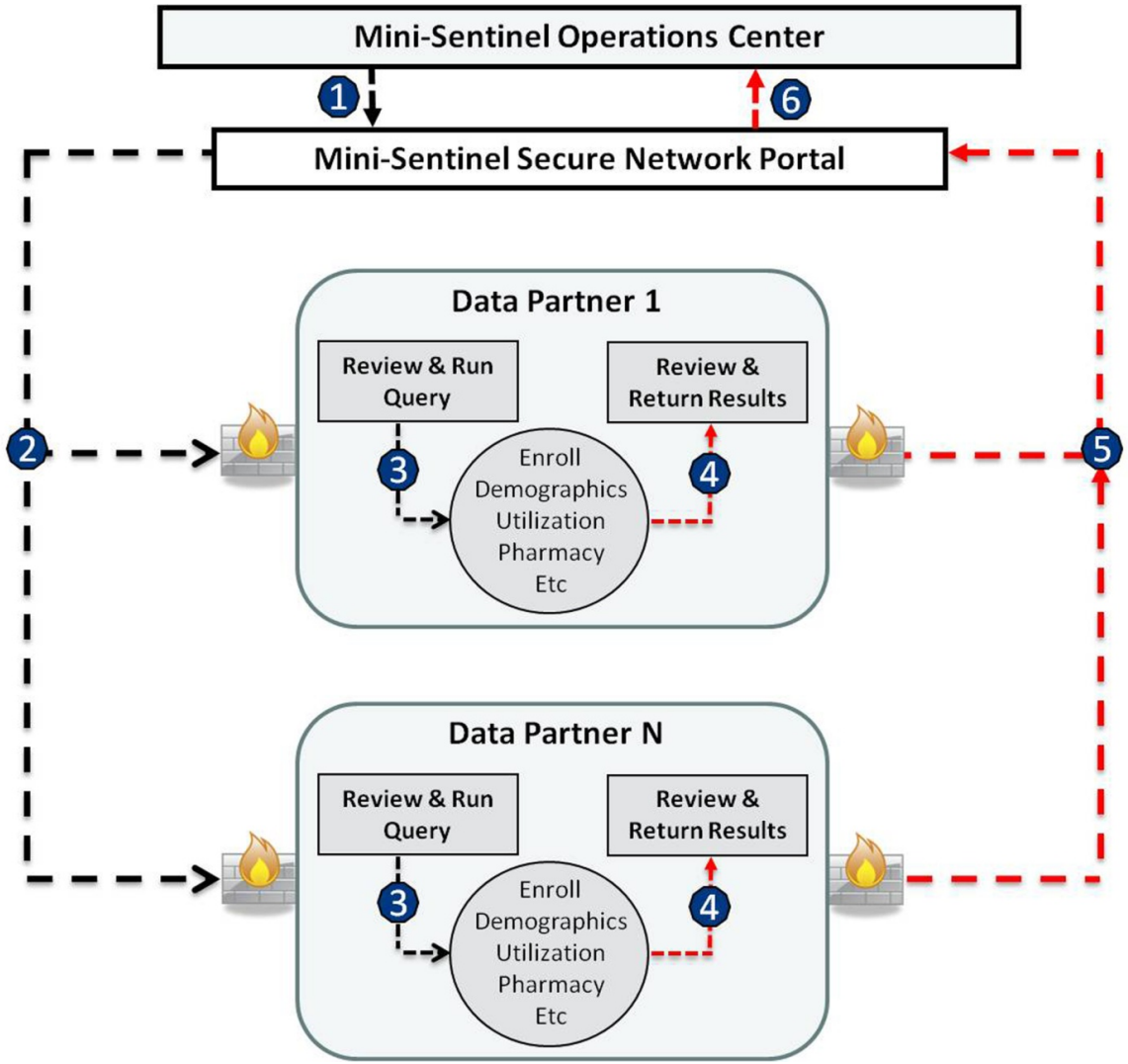
Distributed data system

- Comprised of information held by each data partner. **Each data partner retains physical and operational control over its own data**.
- Requires each data partner to transform its data to a **common data model** based on a standard format according to pre-specified definitions.

Sentinel Common Data Model



Distributed analysis



1- User creates and submits query (a computer program)

2- Data Partners retrieve query

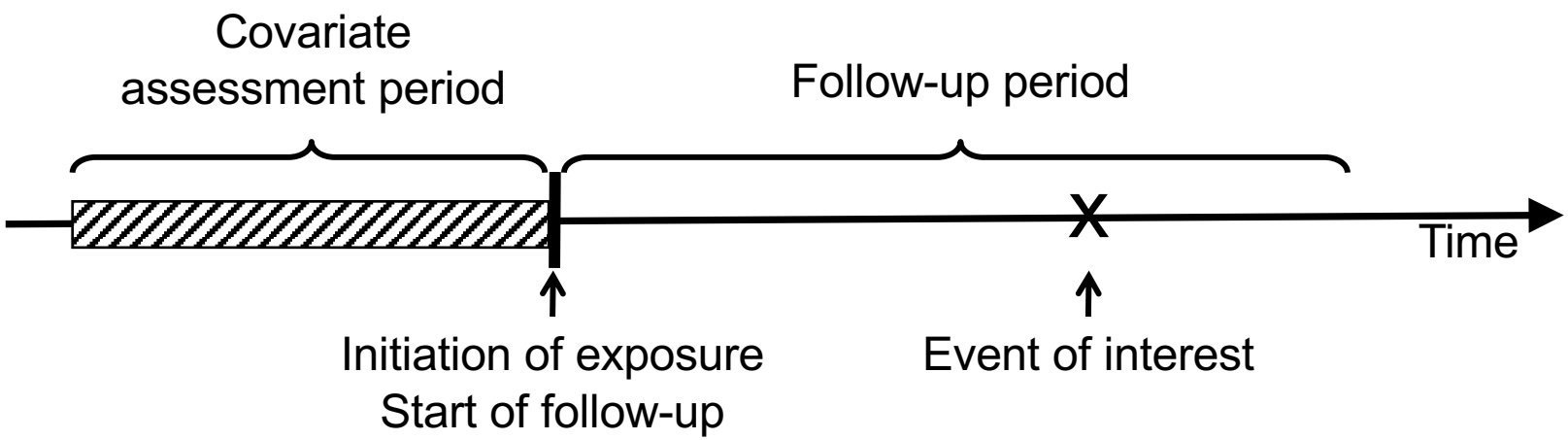
3- Data Partners review and run query against their local data

4- Data Partners review results

5- Data Partners return results via secure network

6 Results are aggregated and returned

PROMPT PS matching



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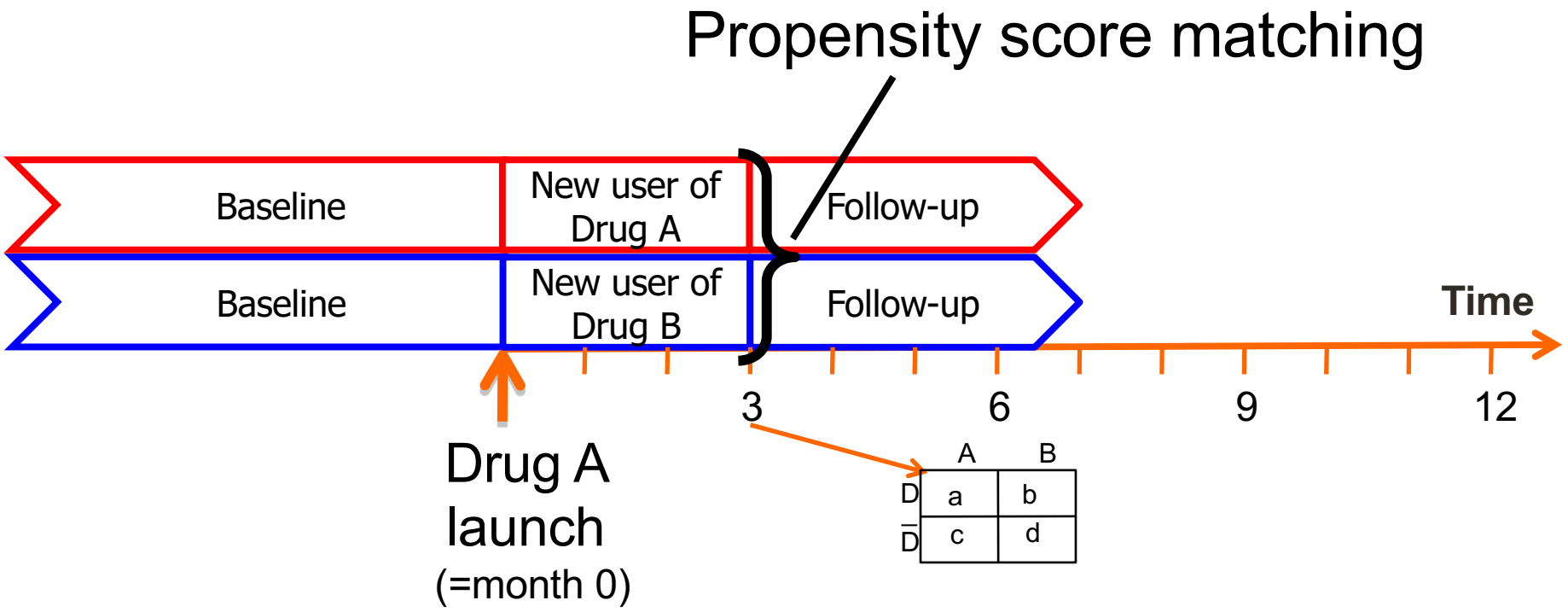
  - Confounding adjustment strategy

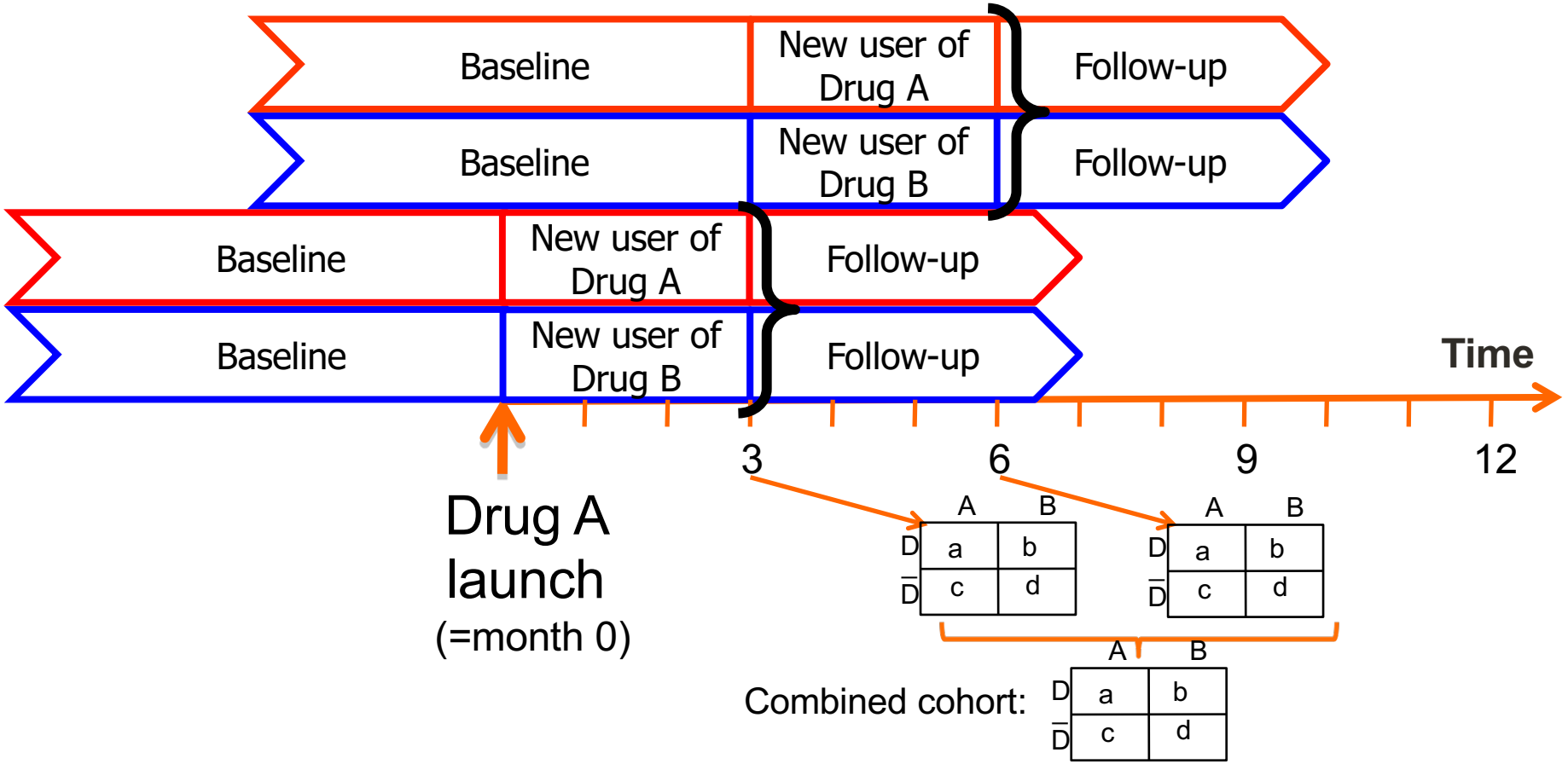
Evidence generation as data refresh
A sequential cohort design



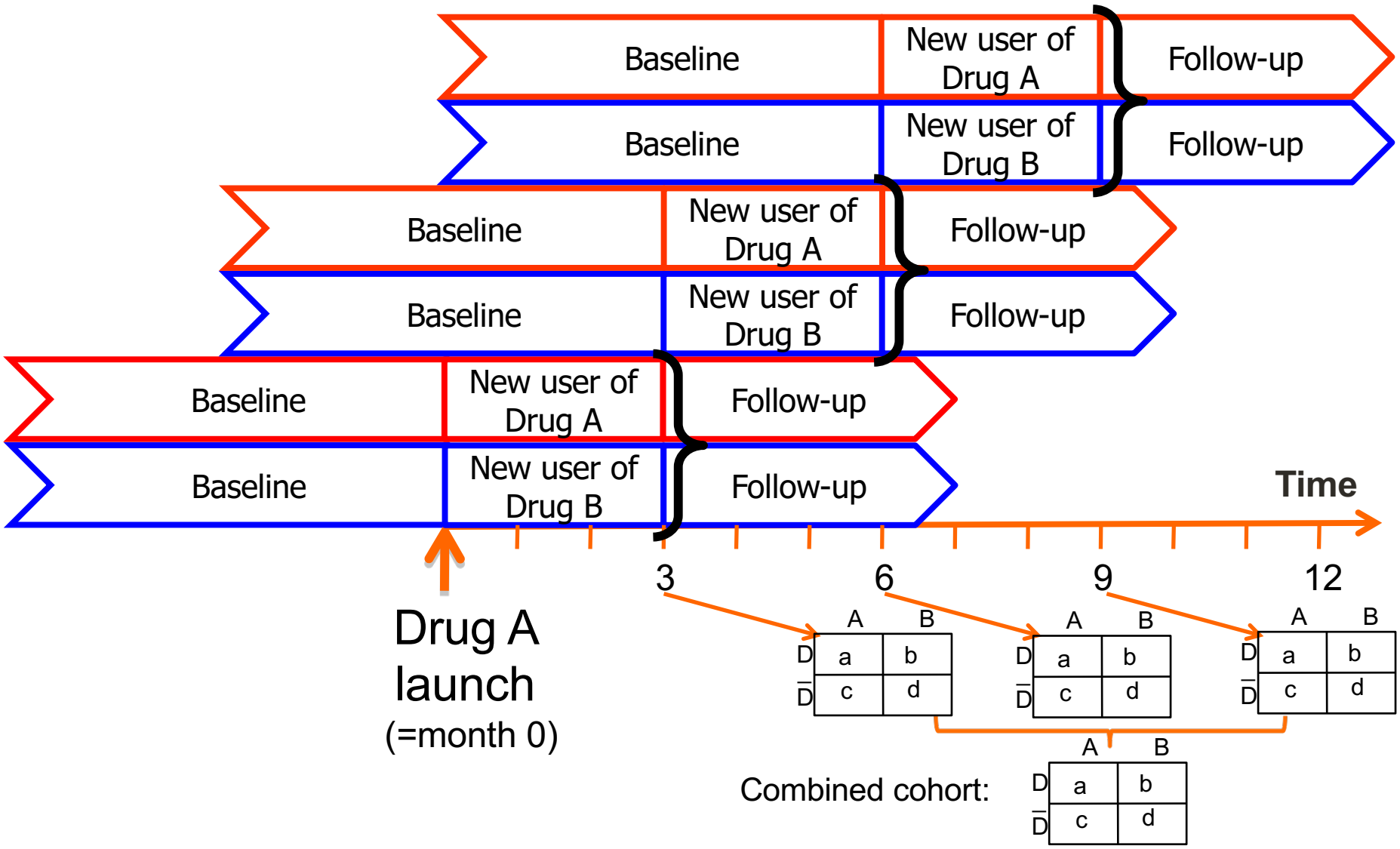
Schneeweiss et al. CPT 2011

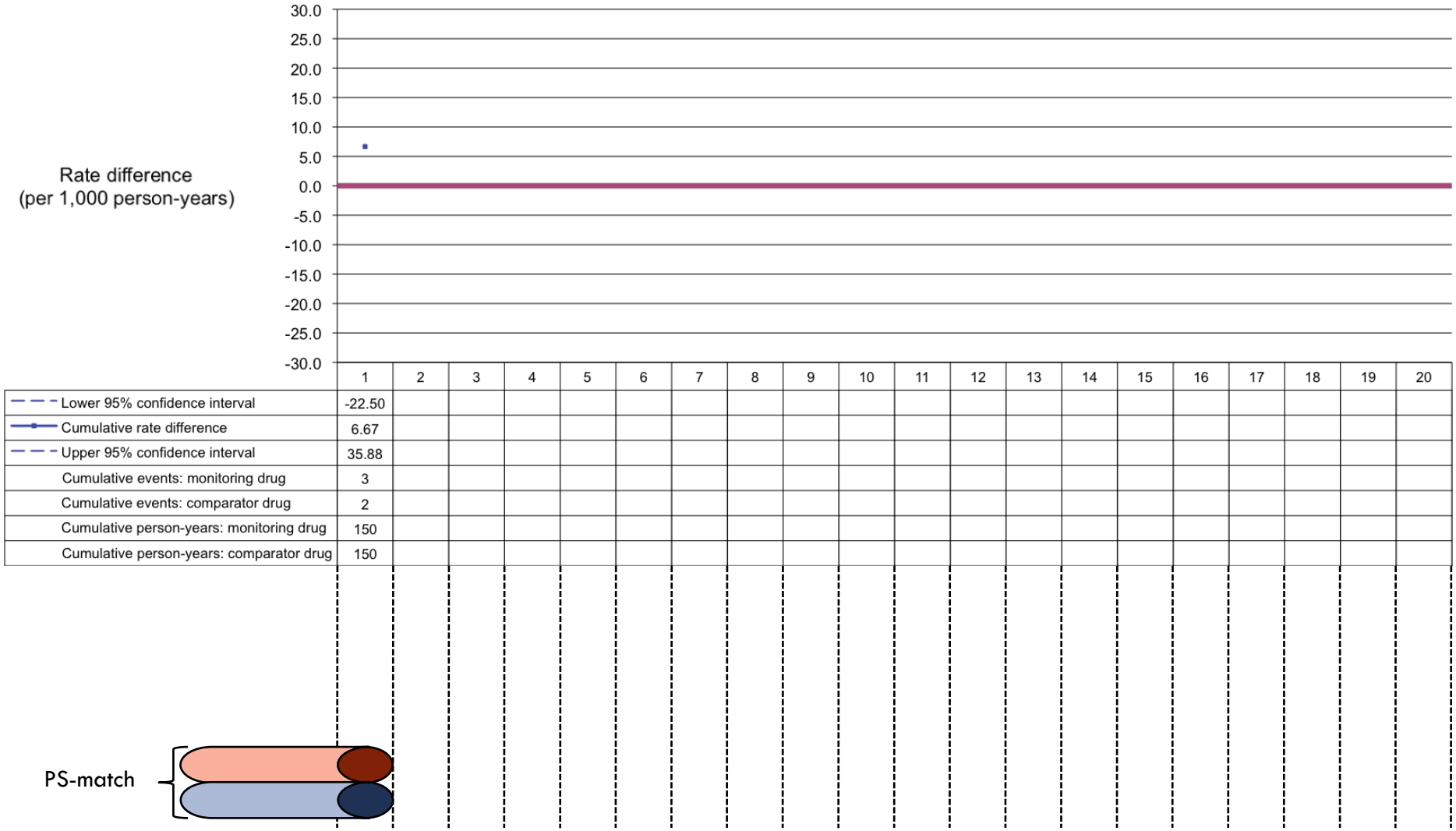
Evidence generation as data refresh
A sequential cohort design

Incorporating data as they accrue:

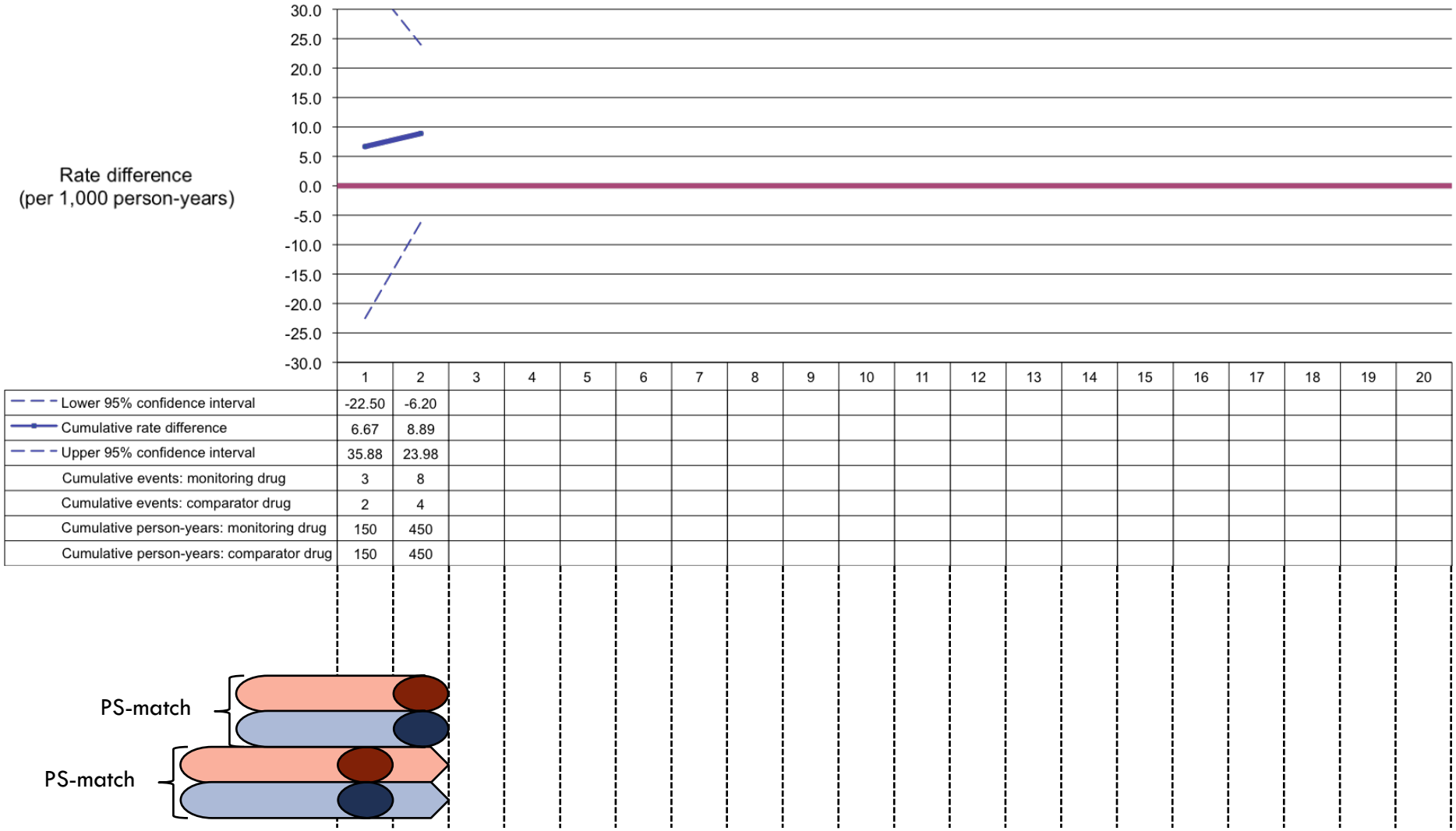


Evidence generation as data refresh
A sequential cohort design

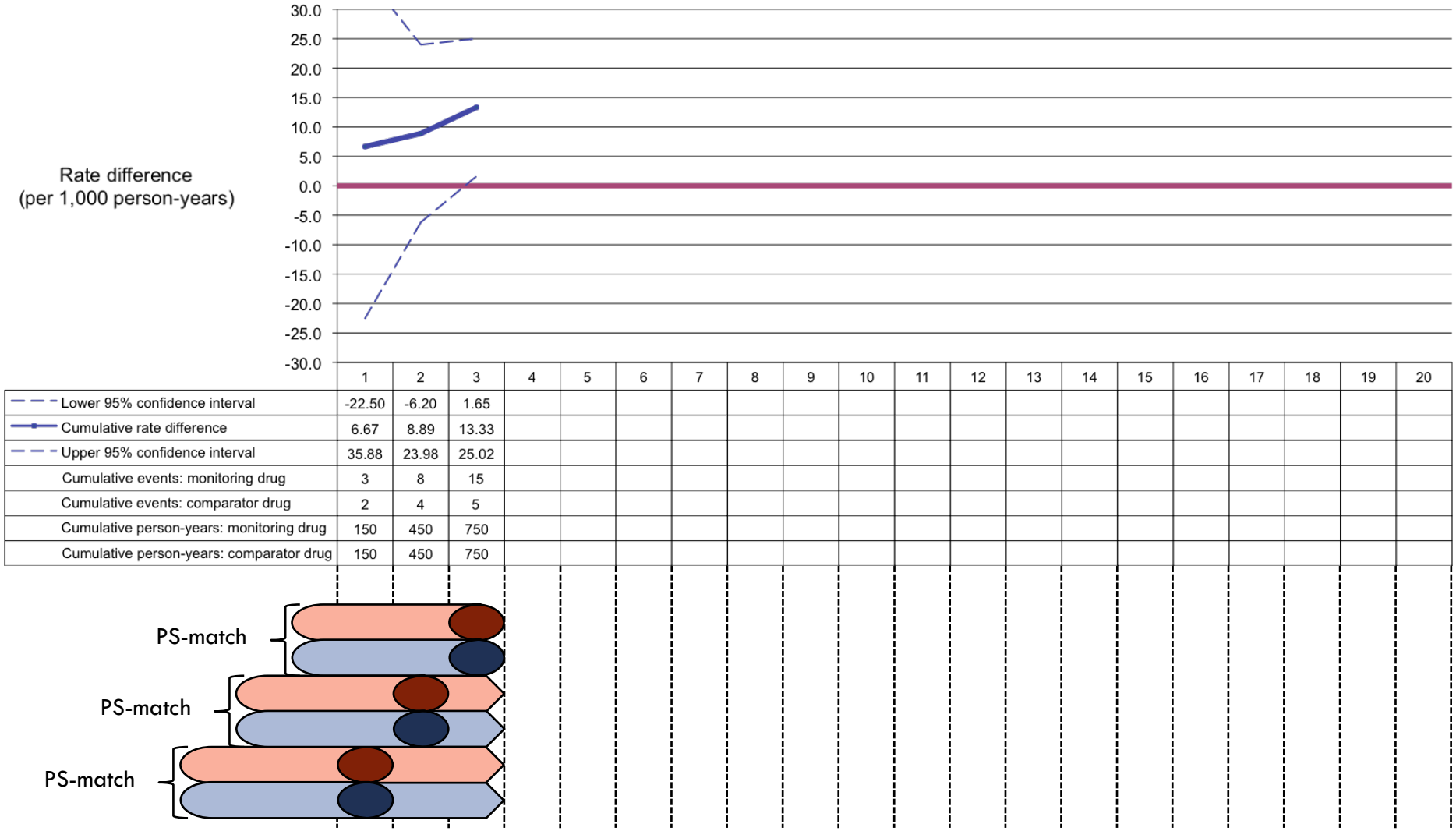




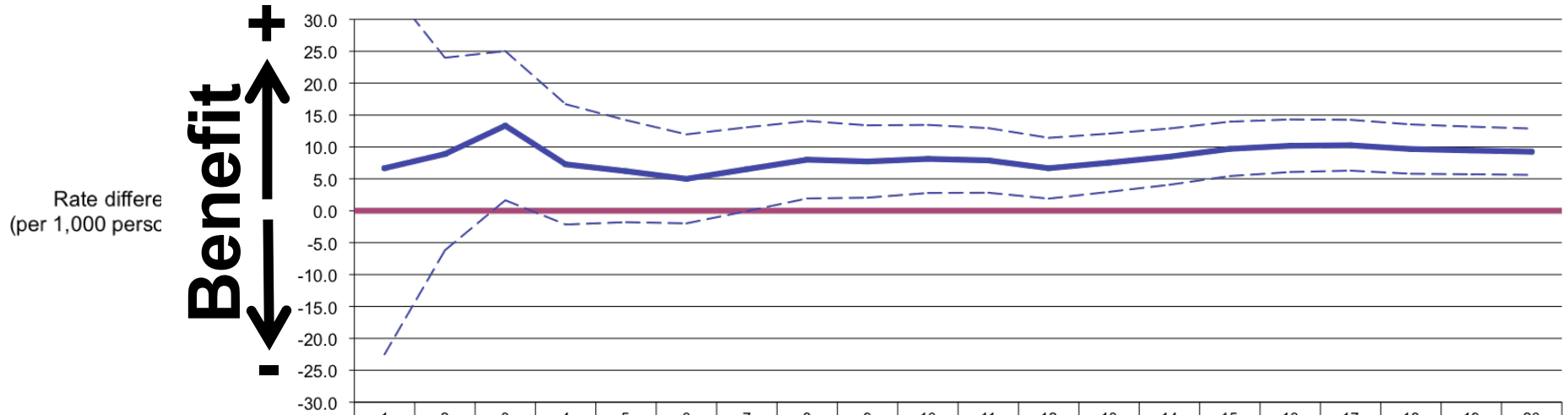
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50																			
Cumulative rate difference	6.67																			
Upper 95% confidence interval	35.88																			
Cumulative events: monitoring drug	3																			
Cumulative events: comparator drug	2																			
Cumulative person-years: monitoring drug	150																			
Cumulative person-years: comparator drug	150																			



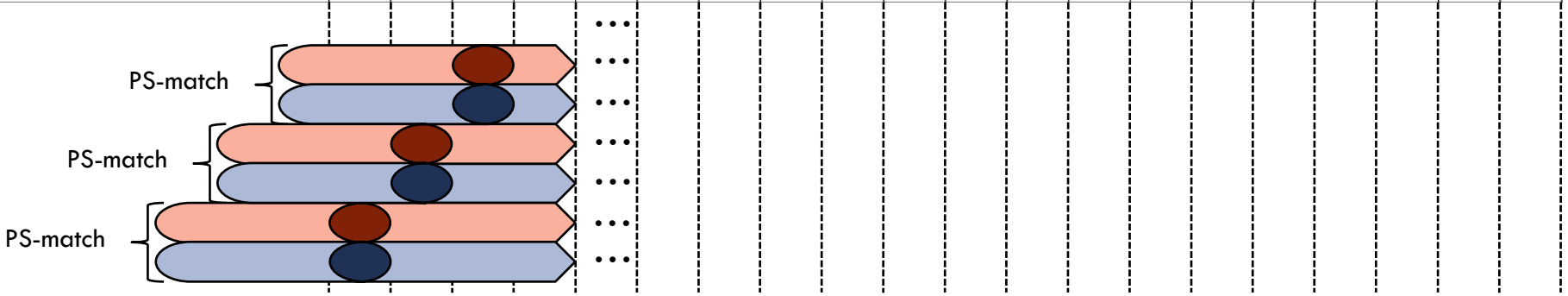
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20																		
Cumulative rate difference	6.67	8.89																		
Upper 95% confidence interval	35.88	23.98																		
Cumulative events: monitoring drug	3	8																		
Cumulative events: comparator drug	2	4																		
Cumulative person-years: monitoring drug	150	450																		
Cumulative person-years: comparator drug	150	450																		



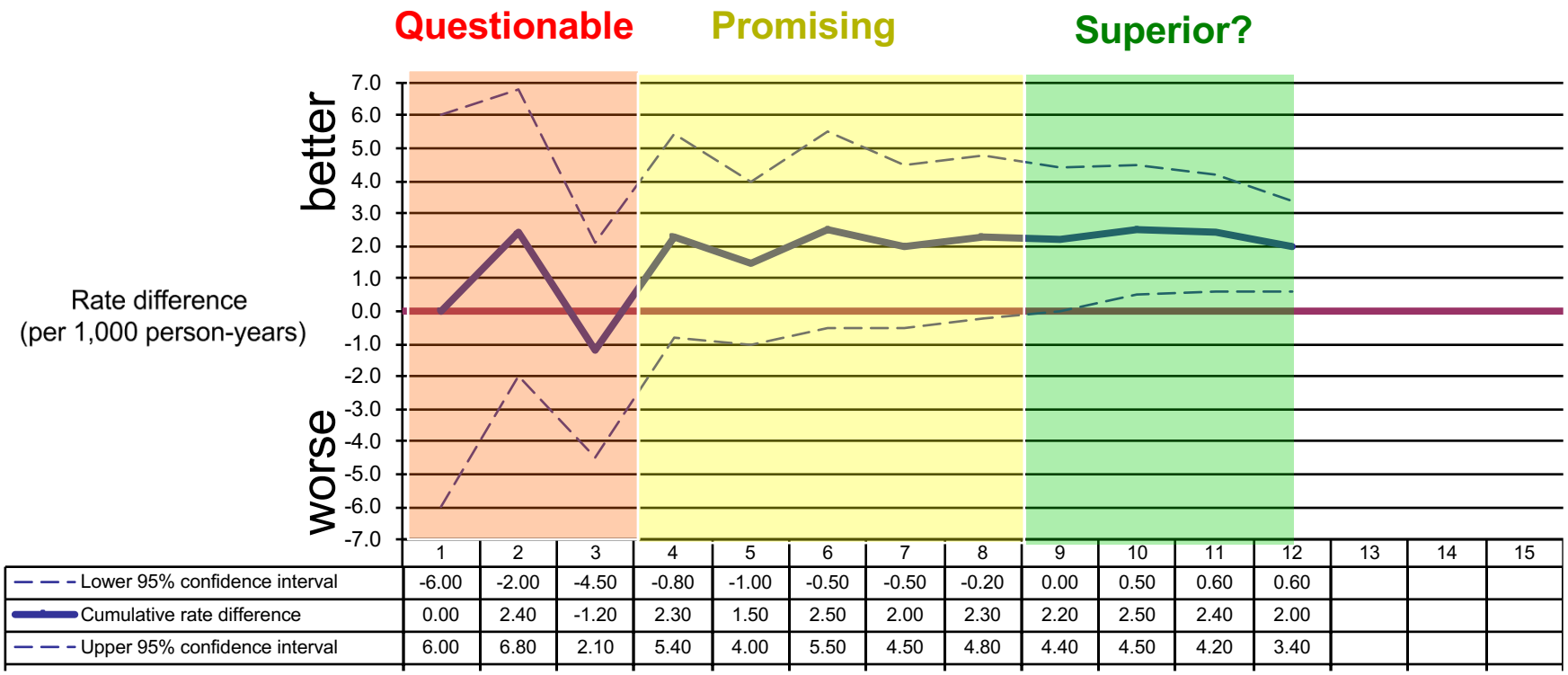
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65																	
Cumulative rate difference	6.67	8.89	13.33																	
Upper 95% confidence interval	35.88	23.98	25.02																	
Cumulative events: monitoring drug	3	8	15																	
Cumulative events: comparator drug	2	4	5																	
Cumulative person-years: monitoring drug	150	450	750																	
Cumulative person-years: comparator drug	150	450	750																	



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lower 95% confidence interval	-22.50	-6.20	1.65	-2.16	-1.79	-1.97	-0.06	1.93	2.05	2.79	2.83	1.90	2.96	4.07	5.43	6.07	6.28	5.80	5.72	5.62
Cumulative rate difference	6.67	8.89	13.33	7.27	6.21	5.00	6.51	8.00	7.72	8.13	7.89	6.67	7.53	8.48	9.70	10.19	10.27	9.67	9.45	9.25
Upper 95% confidence interval	35.88	23.98	25.02	16.70	14.20	11.97	13.08	14.07	13.39	13.46	12.95	11.43	12.09	12.89	13.96	14.31	14.25	13.53	13.18	12.88
Cumulative events: monitoring drug	3	8	15	18	22	25	33	40	45	51	56	58	65	73	82	89	95	99	103	108
Cumulative events: comparator drug	2	4	5	10	13	16	19	20	23	25	28	32	33	34	34	35	37	41	43	46
Cumulative person-years: monitoring drug	150	450	750	1100	1450	1800	2150	2500	2850	3200	3550	3900	4250	4600	4950	5300	5650	6000	6350	6700
Cumulative person-years: comparator drug	150	450	750	1100	1450	1800	2150	2500	2850	3200	3550	3900	4250	4600	4950	5300	5650	6000	6350	6700



Rapid-cycle analytics decision making



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Lower 95% confidence interval	-6.00	-2.00	-4.50	-0.80	-1.00	-0.50	-0.50	-0.20	0.00	0.50	0.60	0.60			
Cumulative rate difference	0.00	2.40	-1.20	2.30	1.50	2.50	2.00	2.30	2.20	2.50	2.40	2.00			
Upper 95% confidence interval	6.00	6.80	2.10	5.40	4.00	5.50	4.50	4.80	4.40	4.50	4.20	3.40			

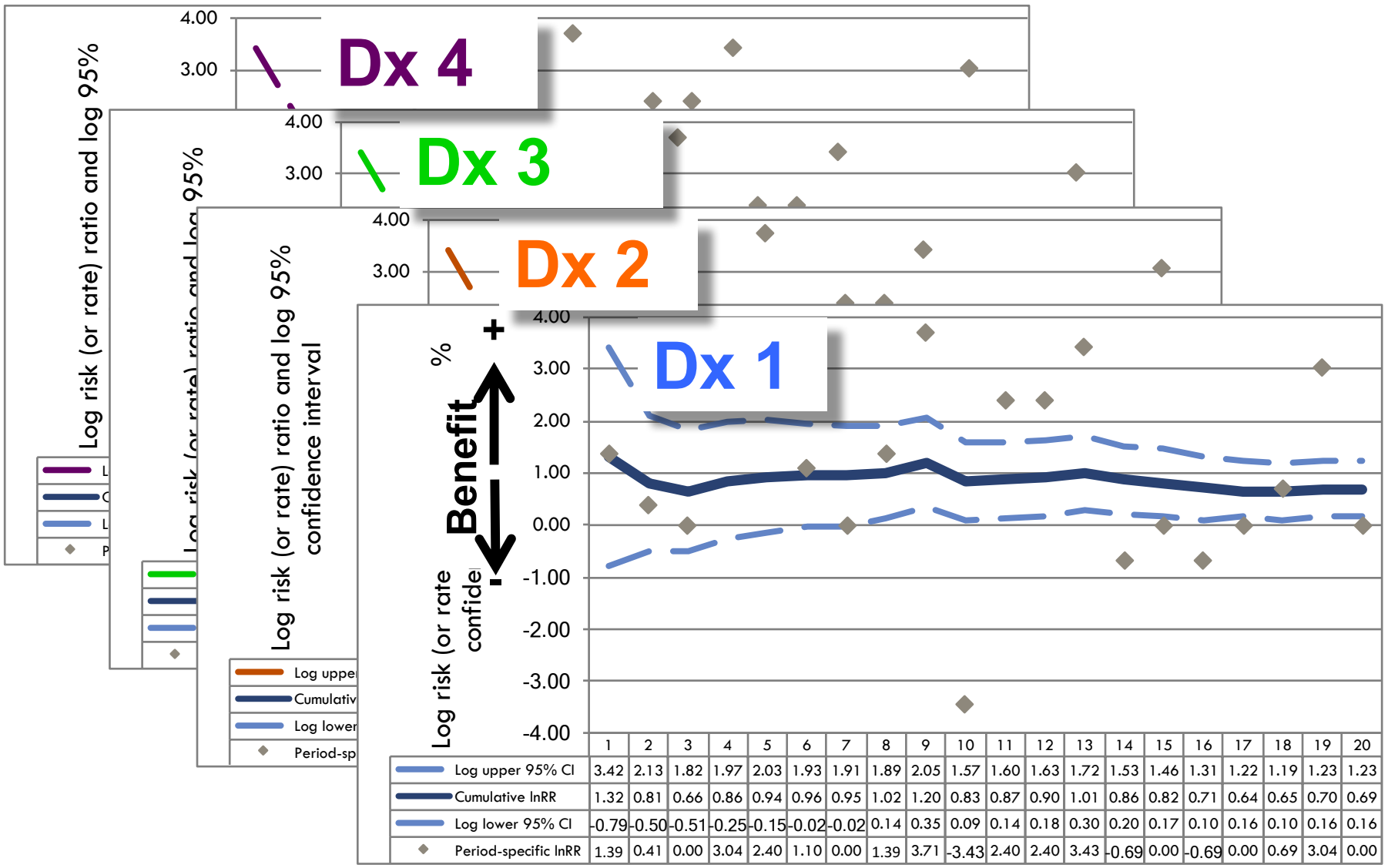
Questionable:
- Investigate subgroup effects
- Continue evaluation

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

Superior:
- Widely disseminate

Schneeweiss, Shrank, Ruhl, Maclure, For the CMS Innovation Center, 2014

Monitoring of multiple endpoints

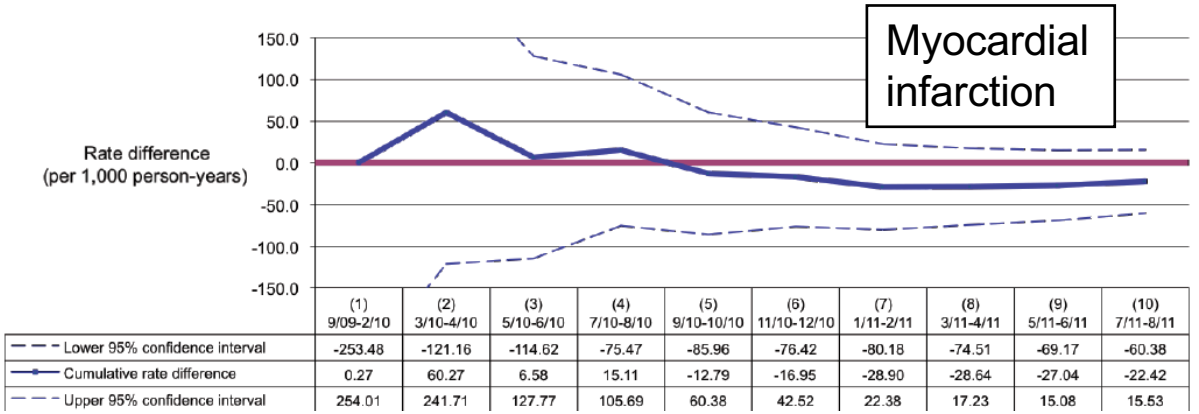


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Log upper 95% CI	3.42	2.13	1.82	1.97	2.03	1.93	1.91	1.89	2.05	1.57	1.60	1.63	1.72	1.53	1.46	1.31	1.22	1.19	1.23	1.23
Cumulative lnRR	1.32	0.81	0.66	0.86	0.94	0.96	0.95	1.02	1.20	0.83	0.87	0.90	1.01	0.86	0.82	0.71	0.64	0.65	0.70	0.69
Log lower 95% CI	-0.79	-0.50	-0.51	-0.25	-0.15	-0.02	-0.02	0.14	0.35	0.09	0.14	0.18	0.30	0.20	0.17	0.10	0.16	0.10	0.16	0.16
Period-specific lnRR	1.39	0.41	0.00	3.04	2.40	1.10	0.00	1.39	3.71	-3.43	2.40	2.40	3.43	-0.69	0.00	-0.69	0.00	0.69	3.04	0.00

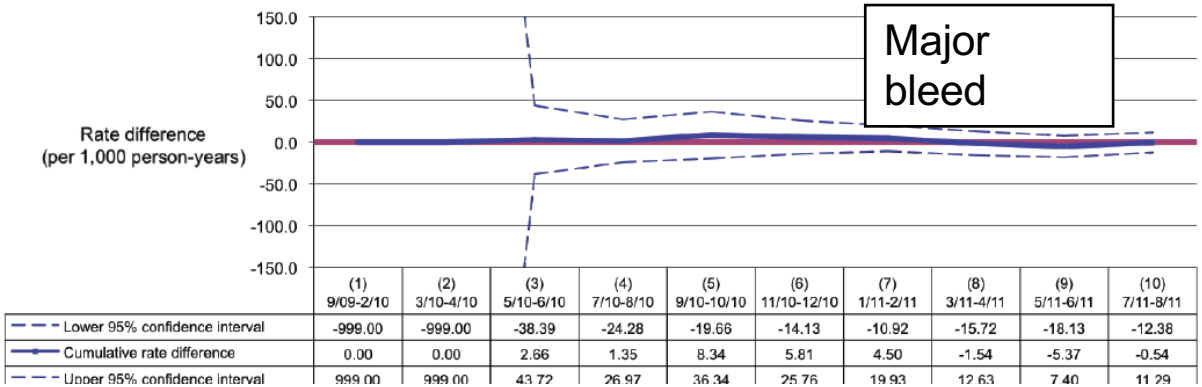
Net benefit

Prasugrel vs. clopidogrel:

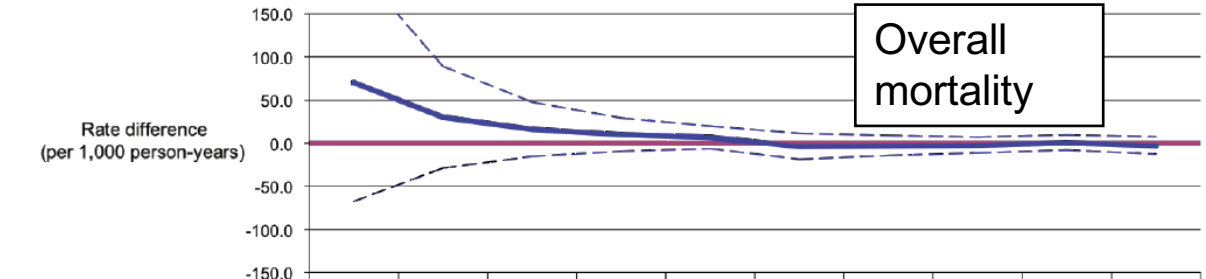
MI prevention vs. bleed



	(1) 9/09-2/10	(2) 3/10-4/10	(3) 5/10-6/10	(4) 7/10-8/10	(5) 9/10-10/10	(6) 11/10-12/10	(7) 1/11-2/11	(8) 3/11-4/11	(9) 5/11-6/11	(10) 7/11-8/11
Lower 95% confidence interval	-253.48	-121.16	-114.62	-75.47	-85.96	-76.42	-80.18	-74.51	-69.17	-60.38
Cumulative rate difference	0.27	60.27	6.58	15.11	-12.79	-16.95	-28.90	-28.64	-27.04	-22.42
Upper 95% confidence interval	254.01	241.71	127.77	105.69	60.38	42.52	22.38	17.23	15.08	15.53



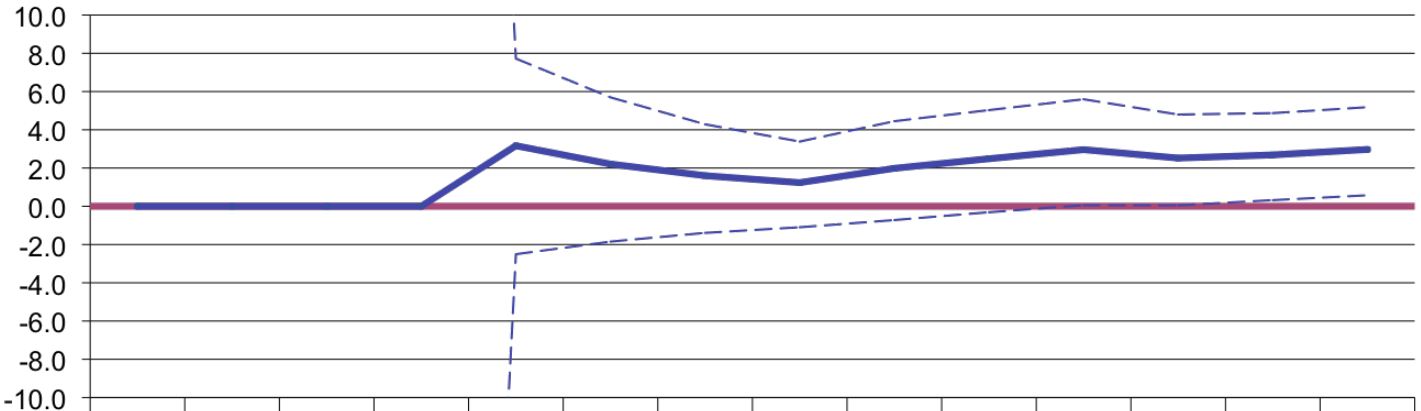
	(1) 9/09-2/10	(2) 3/10-4/10	(3) 5/10-6/10	(4) 7/10-8/10	(5) 9/10-10/10	(6) 11/10-12/10	(7) 1/11-2/11	(8) 3/11-4/11	(9) 5/11-6/11	(10) 7/11-8/11
Lower 95% confidence interval	-999.00	-999.00	-38.39	-24.28	-19.66	-14.13	-10.92	-15.72	-18.13	-12.38
Cumulative rate difference	0.00	0.00	2.66	1.35	8.34	5.81	4.50	-1.54	-5.37	-0.54
Upper 95% confidence interval	999.00	999.00	43.72	26.97	36.34	25.76	19.93	12.63	7.40	11.29



	(1) 9/09-2/10	(2) 3/10-4/10	(3) 5/10-6/10	(4) 7/10-8/10	(5) 9/10-10/10	(6) 11/10-12/10	(7) 1/11-2/11	(8) 3/11-4/11	(9) 5/11-6/11	(10) 7/11-8/11
Lower 95% confidence interval	-67.45	-28.91	-15.41	-9.47	-6.41	-18.63	-14.41	-11.38	-8.11	-12.66
Cumulative rate difference	70.27	30.11	16.05	9.87	6.68	-3.70	-2.85	-2.23	0.57	-2.70
Upper 95% confidence interval	207.99	89.13	47.52	29.20	19.77	11.24	8.70	6.92	9.25	7.26

Gagne et al Drug Saf 2014

Monitoring for rhabdomyolysis among initiators of cerivastatin (Baycol) vs. atorvastatin (Lipitor)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lower 95% confidence interval	-99.00	-99.00	-99.00	-99.00	-2.50	-1.85	-1.39	-1.10	-0.72	-0.31	0.06	0.05	0.32	0.58
Cumulative rate difference	0.00	0.00	0.00	0.00	3.17	2.21	1.60	1.24	1.99	2.49	2.96	2.52	2.69	2.97
Upper 95% confidence interval	99.00	99.00	99.00	99.00	7.72	5.70	4.29	3.38	4.45	5.03	5.60	4.80	4.87	5.18
Cumulative events: cerivastatin	0	0	0	0	1	1	1	1	2	3	4	4	5	6
Cumulative events: atorvastatin	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative person-years cerivastatin	19	60	124	197	316	453	625	809	1007	1206	1350	1586	1861	2019
Cumulative person-years: atorvastatin	26	65	127	218	348	497	681	877	1084	1299	1462	1715	2010	2275

Algorithm 1

Algorithms 2 & 3

Algorithms 4-6

Baycol launched

Rhabdomyolysis added to label

First published case report

Baycol withdrawn

Manufacturer receives 6 case reports

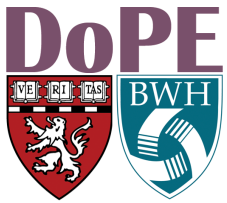
Manufacturer completes observational study that fails to detect association

Conclusions

- Relative absence of studies that directly compare available treatment options in routine care
  - Vs. large number of placebo controlled efficacy trials in highly selected settings
- Effectiveness research using longitudinal healthcare databases can fill this gap
- Systems of networked healthcare databases can serve as national resources for rapid generation of effectiveness and safety evidence, particularly in the context of newly marketed medical products

Thanks!

epatorno@partners.org



Alerting algorithms

Type	Example rules
Fixed nominal Type I error levels	Signal when the exact *p*-value for the cumulative RR < 0.05
Group sequential methods	Pocock or O'Brien-Fleming-like spending functions
Sequential probability ratio tests	maxSPRT
Statistical process control rules	Signal when the test statistic for 4 consecutive period-specific estimates exceed a z-score of 1.0
Estimate-based measures	Signal when 3 consecutive effect estimates exceed some clinically important threshold
Bayesian updating statistics	Signal when 3 consecutive posterior estimates exceed some clinically important threshold